Advances in Methods, Algorithms and Software for Optimization and Simulation of Kidney Paired Donation Programs

by

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To Leann

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TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Figure

ABSTRACT

Kidney Paired Donation (KPD) is a public health initiative wherein kidney transplant candidates with willing but incompatible donors are pooled together with the goal of finding transplant opportunities through the exchange of donors. Transplants are completed either via exchange cycles among incompatible donor-candidate pairs, or by transplant chains initiated by altruistic donors not associated with any particular candidate. Selection of cycles and chains in a KPD program has been modeled as a constrained optimization problem over a directed network, where each vertex represents either a donor-candidate pair or an altruistic donor, and each edge represents a potential transplant between a donor and candidate, weighted by utility (Roth et al., 2007). The goal is to select the disjoint set of cycles and chains that maximize the total utility among the selected transplants. Our aim in this dissertation is to develop and expand existing methods to optimize KPD programs, to generalize concepts and address current realities in KPD management, and to validate these methods through simulation.

In the first project, we consider the issues of uncertainty in transplant viability after selection and recourse to fallback options in cases of non-viability. We extend the standard KPD model to select more general subgraphs of the KPD network, where fallback options consisting of successful sub-cycles and sub-chains can be realized. Methods for determining the appropriate expected utility under uncertainty to assign to such subgraphs are established, through exact calculation

as well as by estimation using Monte Carlo sampling. Simulations of KPD programs are performed, demonstrating a substantial advantage in selecting such subgraphs, in terms of realized utility, compared to the standard KPD model.

In the second project, we generalize the previous formulation to account for candidates joining a KPD program with more than one incompatible donor, introducing additional potential transplant opportunities and fallback options in cases of non-viability. Such KPD models have been sparsely considered in the literature. In this setting, edge properties depend on the specific donor involved, and there exists the possibility of more than one directed edge between two vertices, with implications on the expected utility calculation. We also present a state-transition model for donor and candidate availability within KPD. Through simulation, we demonstrate the benefits of our generalized formulation, not only for individual candidates but for the KPD program as a whole.

In the third project, we investigate temporal aspects of KPD programs, with candidates and donors joining and departing over time, along with matches being confirmed or rejected. We consider modeling the KPD as a 3-dimensional tensor, and decompose the tensor to uncover latent factors within the KPD that allow pairs to be clustered based on their propensity to match with other pairs. This cluster assignment can be used to inform allocation systems, allowing for greater balance between utility and equity. We briefly overview alternative techniques to model the dynamics of KPD programs.

We introduce our software application, which renders an interactive virtual KPD network and incorporates methods developed in this dissertation for research and clinical use. Finally, we outline current realities in KPD management that have yet to be thoroughly explored in the literature as directions for future research.

CHAPTER I

Introduction

1.1 Kidney Paired Donation

For patients with end-stage renal disease, obtaining a kidney transplant is preferable to remaining on dialysis, in terms of both survival and quality of life (Evans et al., 1985; Tamura et al., 2018). While patients in the United States are waitlisted for deceased donor kidney transplantation, there are currently over 95,000 people on this list, with 30,000-40,000 patients being added and only about 15,000 patients receiving a kidney annually (Organ Procurement and Transplantation Network).

Patients with a willing living donor – typically a spouse, relative, or friend – may proceed immediately with transplantation, avoiding a potentially long wait to be allocated a deceased donor kidney. While this represents a viable option for many patients, it is not uncommon for a transplant candidate to be found incompatible with his or her intended donor. This can occur due to blood type incompatibility, or if the immune system of the candidate is sensitized against certain human leukocyte antigens (HLA) of the donor. In these situations, the transplant cannot proceed (Segev et al., 2005b). We refer here to such patients and their donors as incompatible donor-candidate pairs, or "pairs" for short.

While a direct transplant may not be viable for a given donor-candidate pair, it is not difficult to imagine other pairs sharing the same predicament. Suppose there exists a second pair, where the donor is compatible with the transplant candidate of the first pair, and the donor of the first pair is compatible with the candidate of the second. Then a simple exchange of the donors allows each candidate to receive a transplant, thus overcoming each of their own biological incompatibilities for mutual benefit. This exchange is illustrated in Figure 1.1.

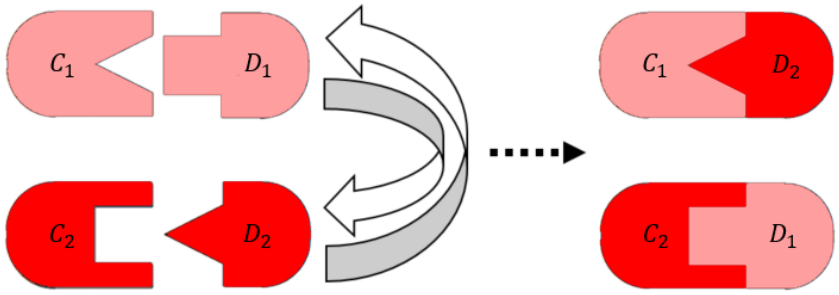


Figure 1.1: Illustration of a typical donor exchange in kidney paired donation. Transplant candidate C_1 is incompatible with their donor D_1, as is candidate C_2 with their donor D_2. Since D_2 is compatible with C_1, and D_1 is compatible with C_2, a simple swap of the donors allows both candidates to receive a transplant.

This idea inspires a system where new transplant opportunities are facilitated by the exchange of donors within a collection of incompatible donor-candidate pairs. This system is referred to as Kidney Paired Donation (KPD). A KPD program, also known as paired kidney exchange program, donor exchange program, or kidney exchange program, consists of a pool of pairs, each comprised of a candidate in need of a kidney transplant along with his or her incompatible donor (or donors). Altruistic donors not associated with any specific candidate, otherwise known as "non-directed donors" (NDD) in the KPD literature, can also participate in KPD programs. KPD is feasible due to the favorable outcomes for living kidney donors, as well as the survival advantage and cost-savings for transplant candidates compared

to continued dialysis (Laupacis et al., 1996; Irwin et al., 2012; Axelrod et al., 2018). According to the Organ Procurement and Transplantation Network, roughly 500-700 transplants have come from KPD programs in the United States annually since 2012, with the figure rising steadily over time.

1.1.1 Brief History

KPD was first proposed by Rapaport (1986), where it was envisioned that two potential recipients with willing but incompatible donors could solve their respective dilemmas by exchanging donors. The first implementation of this idea took place in South Korea (Park et al., 1999). Kidney exchange has since been undertaken in several countries, such as the Netherlands, Canada, the United Kingdom, and Australia, among others (de Klerk et al., 2005; Keizer et al., 2005; Malik and Cole, 2014; Ferrari et al., 2015).

In the United States, under the National Organ Transplantation Act (NOTA), it is illegal for a human to transfer an organ for "valuable consideration". While there had been questions as to whether KPD constituted such valuable consideration, federal legislation explicitly exempting KPD from NOTA was passed in 2007 (Gentry et al., 2011). While most countries operate under a single national KPD registry, in the United States, hospital centers either operate their own programs individually or participate in consortia or networks of KPD programs, possibly concurrently. Examples of such consortia include the National Kidney Registry (NKR) and the Alliance for Paired Donation (APD) (Anderson et al., 2015b; Flechner et al., 2018).

For more information on the history of KPD, the differences in KPD programs across countries, and clinical results from KPD programs, we refer the reader to more comprehensive work on the topic (Montgomery et al., 2005; Wallis et al., 2011; Bingaman et al., 2012; Mierzejewska et al., 2013; Ferrari et al., 2015; Fumo et al.,

2015; Toews et al., 2017). Additional information on the fundamental aspects and limitations of KPD can be found in (Gentry et al., 2011).

1.1.2 Transplant Mechanisms - Cycles and Chains

We describe here two mechanisms to realize transplants in KPD. In each of these mechanisms, transplants are arranged so that the candidate in each pair is matched with a donor who is expected to be immunologically compatible based on an assessment of certain characteristics, namely the blood type combination and the sensitivity of the candidate to donor HLA. Preferences of the donors, candidates and transplant centers involved are also considered when determining potential transplants. This preliminary assessment of compatibility is referred to as the virtual crossmatch.

In an exchange cycle of size ℓ, or ℓ-way exchange, the donor from one pair donates to the candidate in the next pair along the cycle, with the final ℓ-th donor closing the cycle by donating to the original candidate. The simple donor swap in Figure 1.1 is an example of a cycle of size 2, or 2-way exchange. Figure 1.2 illustrates an example of a cycle of size 3, or 3-way exchange.

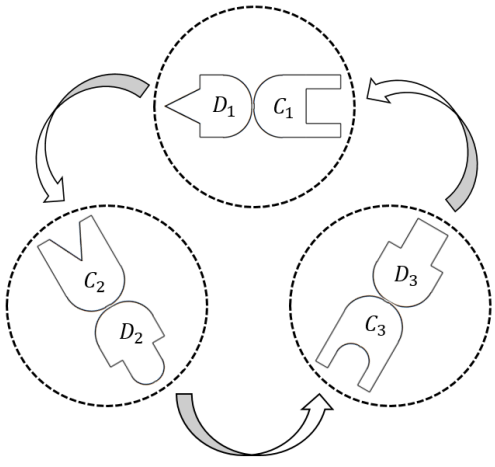


Figure 1.2: Example of an exchange cycle of size 3 involving three incompatible donor-candidate pairs.

In cycles, there is the practical limitation that all transplants must be performed simultaneously in order to avoid the possibility of a scheduled donor reneging on their commitment after their candidate has received their transplant. Without this restriction, the possibility exists that a donor will have donated a kidney without their candidate having obtained a transplant. For this reason, if any one of the transplants in a proposed cycle are later found to be unsuitable for transplantation, none of the selected transplants in the cycle can proceed. Thus, cycles are often limited in size, typically to 2 or 3 pairs, due to the logistics involved in practice.

A transplant chain of length ℓ in KPD is initiated by a NDD, who voluntarily donates to a candidate in the pool. The donor associated with the transplanted candidate goes on to donate to another candidate in the pool, whose donor donates to another candidate, and so on for a total of ℓ transplants (Roth et al., 2006). See Figure 1.3 for an example of a transplant chain of length 2. Matching a NDD to an incompatible pair in KPD, as opposed to direct allocation to a transplant candidate on the deceased donor waitlist, effectively multiplies the gift of the donor by allowing more than one patient to obtain a transplant (Gentry et al., 2009).

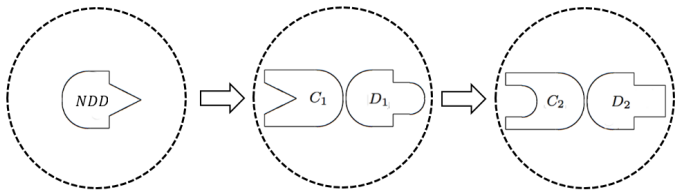


Figure 1.3: Example of a transplant chain of length 2 involving a NDD and two incompatible donor-candidate pairs.

Two strategies for including NDDs in KPD programs have been previously described in the literature. In Domino Paired Donation (DPD), a short transplant chain involving one or two incompatible pairs, generally transplanted simultaneously, ends with the final donation to a candidate on the deceased donor

waitlist (Montgomery et al., 2006). In Non-simultaneous Extended Altruistic Donation (NEAD), chains extend as the final donor from each chain segment is retained as a bridge donor, who are eligible to continue the chain at a later time (Rees et al., 2009). For example, in Figure 1.3, the final donor D_2 can act as a bridge donor and initiate additional chain transplants sometime in the future. The merits and pitfalls of each strategy are explored in Gentry et al. (2009). In this dissertation, we will generally focus on chains arranged via the NEAD strategy.

There are several advantages to chains in comparison to cycles. First, each donor in a chain can donate to any other compatible transplant candidate in the pool, without requiring a reciprocal match back to an original candidate (Melcher et al., 2013b). Also, transplant chains can be performed non-simultaneously, as donors donate only after their paired candidate has received their transplant (Rees et al., 2009; Dickerson et al., 2016). Thus, while having a donor renege on their commitment in the middle of a chain would be unfortunate, it would not irreparably harm the remaining pairs in the chain, as no donor will have donated without their paired candidate having first received their transplant (Cowan et al., 2017). In the NKR experience, many donors remain motivated to donate, in some cases months after their paired candidate received their transplant (Melcher et al., 2012). Several studies have explored ethical issues with respect to non-directed donation, including the risk of donors reneging on their commitment, as well as whether such chains disadvantage candidates, notably those with O blood type, on the deceased donor waitlist (Adams et al., 2002; Sharif, 2013; Wall et al., 2017).

1.2 Mathematical Formulation of Kidney Paired Donation

The overarching goal in KPD is to select the most desirable set of kidney exchanges to evaluate for transplantation among the many possible alternatives at any given time. Note that each pair or NDD can participate in at most one cycle or chain, as each individual donor can only donate one kidney. Traditionally, a KPD pool is managed through a sequence of regularly scheduled evaluations, referred to as match runs, wherein the pool is assessed and a solution consisting of cycles and chains is determined. Match run schedules vary by program, with match runs taking place roughly every 3-4 months in some national programs to daily match runs in smaller centers (Ferrari et al., 2015). Even in modestly-sized pools, there will typically be a number of overlapping cycles and chains, and consequently many possible solutions.

The preferred solution would ideally be determined by pre-specified objectives, such as maximizing the total number of transplants achieved. More generally, matches between donors and candidates can each be assigned a utility, representing the clinical value of the associated transplant relative to others, should it be realized. The preferred solution would then maximize the total utility of the selected transplants. Typically, each match is weighted equally, effectively with a value of 1, representing the one potential transplant associated with the match. Alternatively, transplant centers have developed scoring systems to give precedence to certain matches, such as those involving highly-sensitized, pediatric, or medically urgent candidates, or to preserve blood type O donors for blood type O recipients (Melcher et al., 2013a).

The KPD problem has been modeled and analyzed under a variety of settings (Roth et al., 2004, 2005b; Segev et al., 2005a). In this dissertation, we focus primarily

on the novel integer linear programming formulation proposed initially by Roth et al. (2007). This formulation allows one to easily model a number of variations on the objective, and to add additional constraints to the problem.

The KPD pool is modeled as a directed graph $G = (V, E)$. Here, $V = V^P \cup V^A$ denotes the set of vertices, which in this setting comprise the set of incompatible donor-candidate pairs, V^P, and the set of NDDs, V^A (where A stands for "altruistic"). The edge set, representing matches, or potential transplants based on the results of virtual crossmatches, is given by:

$$E = \{(i, j) : i \in V, j \in V^P, i \neq j, \\ \text{successful virtual crossmatch from donor of } i \text{ to candidate of } j\}. \tag{1.1}$$

An exchange cycle $c = (V_c, E_c)$ of size ℓ can then be defined as a subgraph of G, such that $V_c = \{i_1, i_2, \ldots, i_\ell\}$, where $i_1, i_2, \ldots, i_\ell \in V^P$, and $E_c = \{(i_k, i_{k+1}) : k = 1, 2, \ldots, \ell-1\} \cup (i_\ell, i_1) \subseteq E$. A chain $c' = (V_{c'}, E_{c'})$ of length ℓ can be similarly defined as a subgraph of G, such that $V_{c'} = \{i_0, i_1, i_2, \ldots, i_\ell\}$, where $i_0 \in V_A$, $i_1, i_2, \ldots, i_\ell \in V^P$, and $E_c = \{(i_k, i_{k+1}) : k = 0, 1, 2, \ldots, \ell - 1\} \subseteq E$. We will also use the following notation occasionally, which follows from the previous formulation. We indicate a cycle of size ℓ by the ordered ℓ-tuple $c = \langle i_1, \ldots, i_\ell \rangle$, $i_1, i_2, \ldots, i_\ell \in V^P$, which indicates that the donor of pair i_k matches with the candidate of pair i_{k+1} for $k = 1, \ldots, \ell - 1$, and the donor of pair i_ℓ matches with the candidate of pair i_1. Similarly a chain of length ℓ is denoted by the ordered $(\ell+1)$-tuple $c' = \langle i_0, i_1, \ldots, i_\ell \rangle$, $i_0 \in V^A$, $i_1, i_2, \ldots, i_\ell \in V^P$, where NDD i_0 matches with the candidate of pair i_1, and the donor of pair i_k matches with the candidate of pair i_{k+1} for $k = 1, \ldots, \ell - 1$.

For edge $e = (i, j) \in E$, let $u_e \equiv u_{ij} \in \mathbb{R}^+$ be the utility associated with the transplant between the donor of i and the candidate of j. The total utility of cycle $c = (V_c, E_c)$ is given by the sum of its constituent edge utilities, such that $U_c =$

$\sum_{e \in E_c} u_e$. The utility of a potential solution C^* is then simply the sum of the utilities of its constituent cycles, i.e. $\sum_{c \in C^*} U_c$. Let $\mathcal{C}$ be the set of cycles under consideration. For each $i \in V$, let $\mathcal{C}_{(i)}$ denote the set of cycles in $\mathcal{C}$ that involve pair i, i.e. $\mathcal{C}_{(i)} = \{c \in \mathcal{C} : i \in V_c\}$. Let $Y_c = \mathbb{1}(\text{cycle } c \text{ selected for transplantation})$. The problem of selecting the maximum utility cycle solution, the preferred solution for transplantation, is given by the following integer programming (IP) problem:

$$\begin{aligned} &\max_{\{Y_c\}} \sum_{c \in \mathcal{C}} Y_c U_c \\ &\text{subject to} \sum_{c \in \mathcal{C}_{(i)}} Y_c \leq 1, \forall\ i \in V, \\ &Y_c \in \{0,1\}, \forall\ c \in \mathcal{C}. \end{aligned} \tag{1.2}$$

Note that chains can be handled effectively in the same manner as exchange cycles in the standard model (1.2) by including implicit "back-edges" from every pair in the pool back to each NDD, thus converting the chain into an artificial cycle. See Figure 1.4 for an illustrative diagram. Based on this property, we will sometimes use the term "cycles" in this dissertation to refer to both exchanges cycles and transplant chains, though we will make clear when these should be considered together or separately.

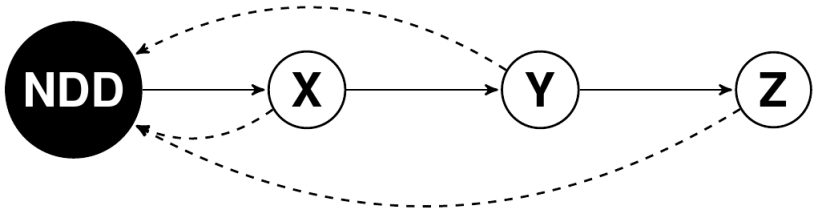


Figure 1.4: Example of a chain of length 3 consisting of a NDD, in black, and three pairs represented by vertices labeled X, Y, and Z. The dashed arrows represent back-edges. Three artificial cycles are effectively induced in this chain using the back-edge formulation.

Figure 1.5 depicts a typical solution within a KPD network. The maximum utility cycle formulation can be solved in polynomial time when the cycle size is restricted to 2, as the problem reduces to a maximum weight matching problem on an undirected graph (Abraham et al., 2007). There also exists an edge formulation, which can be solved in polynomial time when there are no constraints on the cycle size, by reducing to a maximum weighted perfect matching problem on a bipartite graph. If, however, cycles are capped at some length L, where L is an integer greater than 2 but less than the number of participating pairs, this IP problem is NP-hard (Roth et al., 2007). Thus, while it has been shown that it is preferable to admit both 2- and 3-way exchanges (such that $L = 3$) in KPD over 2-way exchanges alone (such that $L = 2$), even this case may be computationally burdensome (Saidman et al., 2006). Practically, solutions for such IP problems can be obtained with the aid of optimization software, such as CPLEX or Gurobi, for pools of modest size. In this dissertation, we use Gurobi exclusively for optimization (Gurobi Optimization Inc.).

1.3 Objectives

This dissertation is a spiritual successor to that of Li (2012), developing and expanding on ideas initially presented there. In this dissertation, we establish and propose significant improvements to methods and algorithms that account for the inherent uncertainty in KPD and allow for fallback options in the cases of non-viability, address several current issues that are of clinical importance to KPD, such as candidates joining with more than one donor and difficult-to-match pairs accumulating in KPD pools over time, and demonstrate our improvements using simulations and visual software.

This dissertation is organized as follows. In Chapter II, we propose to account

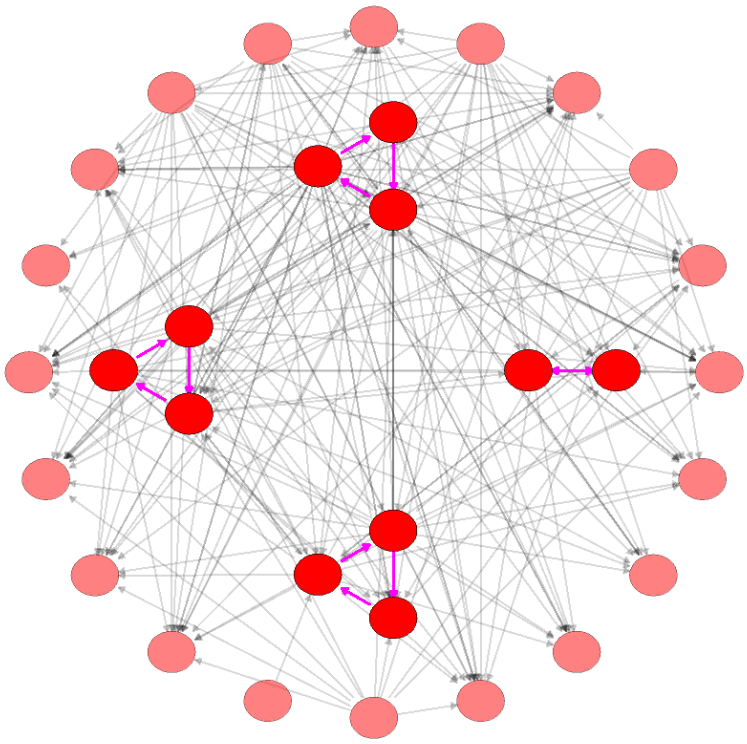


Figure 1.5: Example of a KPD network, consisting of incompatible donor-candidate pairs as vertices and matches between donors and candidates as edges, with a solution centered and highlighted.

for uncertainty in transplant viability, as well as for fallback options in cases of such uncertainty, culminating in a divide-and-conquer approach focusing on dense subgraphs of the KPD network. In Chapter III, we extend and generalize the KPD formulation to account for pairs joining KPD with more than one incompatible donor. In Chapter IV we model the temporal aspects of a KPD program via a 3-dimensional tensor, and attempt to uncover latent features of the underlying network over time through tensor decomposition, with the goal of achieving a greater balance between utility and equity in transplantation. We present our software application implementing elements of this dissertation in Chapter V, and conclude with a discussion of additional issues in KPD in Chapter VI.

CHAPTER II

Uncertainty and Fallback Options in Kidney Paired Donation

2.1 Introduction

The formulation presented in Section 1.2 to select the optimal set of disjoint chains and cycles assumes all selected transplants will proceed to transplantation without issue. In reality, there is non-negligible uncertainty in every step of a KPD program, and there exists the possibility, should certain exchanges be found non-viable, that selected cycles and chains may have to be abandoned or shortened. By accounting for this uncertainty, we can instead attempt to select exchanges that are the most likely to lead to successful transplants, and that allow for immediate recourse to fallback options in cases of non-viability.

2.1.1 Uncertainty in Transplant Viability

Candidate sensitivity to foreign HLA is a major barrier to successful kidney transplantation, with many patients having pre-formed sensitivities to certain donor antigens (Mierzejewska et al., 2013; Zecher et al., 2018). In first-time transplant recipients, such sensitization arises as a result of pregnancies, blood transfusions, and pathogen exposure. In repeated transplant recipients, sensitization occurs due to previous graft exposure (Velidedeoglu et al., 2018).

Initially, matches between donors and candidates that are expected to be biologically compatible are determined by virtual crossmatch based on the blood type combination, known information on candidate sensitivities to donor HLA, and preferences of the donors, candidates and transplant centers. However, comprehensive compatibility testing, where antibodies against a specific donor are detected by incubating candidate serum with donor lymphocytes, can uncover incompatibilities that had not been previously detected. This laboratory crossmatch must take place before a donor and candidate proceed to transplantation, in order to confirm the viability of the transplant. In other words, though a virtual crossmatch is negative, indicating a presumed viable transplant, the result can be overturned if a clinically relevant HLA mismatch is revealed in a positive laboratory crossmatch (Johnson et al., 2016). Failure to proceed with an exchange can also occur if a candidate or transplant center declines the proposed donor, or if a selected donor or candidate must withdraw from the pool, for example due to illness, either temporarily or permanently (Fumo et al., 2015). Note that when we use the term "failure" in this context, we are referring to the failure of a selected donor, candidate, or match proceeding to transplantation, not to kidney graft failure.

The discovery of additional candidate sensitivities, or other situations where selected pairs cannot proceed with transplantation, means that one can realistically expect only a fraction of patients among the selected exchanges to receive the kidney they were originally allocated (Dickerson et al., 2013). If a proposed transplant were found to be non-viable within a cycle, none of the transplants in the cycle would be able to proceed, as that would require a donor to undergo transplantation without their paired candidate receiving their promised transplant.

Similarly, chains cannot advance to completion as initially determined, though it may be administratively permissible for transplantation to proceed up to the point of failure, as no donor will have donated without their candidate first receiving a transplant (Montgomery et al., 2006; Roth et al., 2006; Rees et al., 2009).

Several studies have proposed to move away from the deterministic model of KPD to a model incorporating stochastic elements, where the operational uncertainty in arranging kidney exchanges is addressed by considering the probabilities that selected exchanges are found to be non-viable prior to transplantation (Chen et al., 2012; Dickerson et al., 2013; Li et al., 2014b; Pedroso, 2014). In Li (2012), each match is assigned a probability corresponding to the chance that the match is proven viable. For $e \in E$, let X_e represent the Bernouilli random variable describing the event the match is truly viable, and let $p_e = P(X_e = 1)$. The probability an exchange cycle c is viable is therefore given by $P_c \equiv \prod_{e \in E_c} p_e$. Note that it is assumed that match failures are independent. The expected utility of the cycle is therefore given by $EU_c \equiv P_c U_c$, and the total expected utility of the solution $\mathcal{C}^*$ is given by $\sum_{c \in \mathcal{C}^*} EU_c$. By substituting EU_c for U_c in (1.2), the problem becomes one of maximizing the expected utility among disjoint cycles and chains, as opposed to the (presumed) utility.

2.1.2 Fallback Options for Non-Viable Exchanges

One concern when dealing with the uncertainty inherent in KPD is the re-allocation of pairs and NDDs when planned exchanges fail. In the case of such a failure, there may be an opportunity for immediate recourse to alternative transplant options. In particular, within a chosen cycle or chain, one can immediately consider for transplantation any sub-cycle or sub-chain that remains viable once failures in the originally selected cycle or chain are determined (Li,

2012; Li et al., 2014b).

An example of a fallback option in a 3-way exchange is illustrated in Figure 2.1. In Figure 2.1(a), we observe three pairs forming a cycle, from pair A to B to C and back, with an additional match identified from the donor of pair B to the candidate of pair A. If the match between the donor of pair B and the candidate of pair C were to be overturned based on the results of a laboratory crossmatch, as illustrated in Figure 2.1(b), or if either the donor or candidate in pair C were to withdraw after selection or the match between the donor of pair C and the candidate of pair A were to be overturned, one would still be able to revert to the 2-way exchange between pairs A and B as a fallback option.

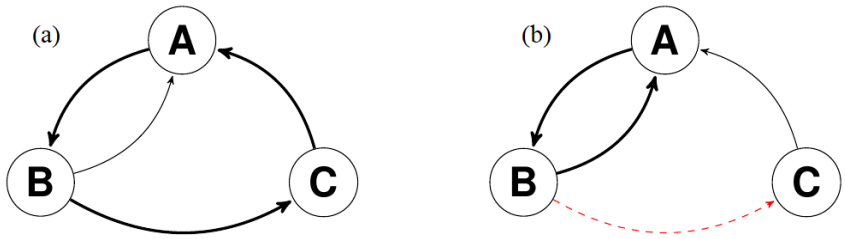


Figure 2.1: Example of (a) a 3-way exchange between pairs A, B, and C, and (b) a fallback option to a 2-way exchange between pairs A and B in the event of failure.

Strategies that include fallback options operate under the assumption that after confirming availability of donors and candidates, as well as the viability of all matches within the original cycle or chain, one would proceed to transplantation with the optimal set of remaining sub-cycles and sub-chains. Previous studies have considered contingency planning early in the selection stage, though mostly restricted to simple cycles (Li et al., 2014b; Klimentova et al., 2016; Alvelos et al., 2016). Their work motivates our contributions here.

2.1.3 Outline

We consider a KPD program consisting of both donor-candidate pairs and NDDs, and propose separating the sources of failure in the matches from those pertaining to the pairs or NDDs. We also identify a more general class of transplant arrangements that allows for additional fallback options to be considered during optimization. We then describe methods to assign an appropriate expected utility value to each such arrangement. Simulations demonstrate the superiority of our approach in a realistic dynamic model of KPD.

2.2 Adapting Kidney Paired Donation to Account for Uncertainty and Fallback Options

Following Section 1.2, we represent the pairs and NDDs and the matches between them as a directed graph $G = (V, E)$, with vertex set $V = V^P \cup V^A$ comprising the set of donor-candidate pairs, V^P, and the set of NDDs, V^A. The edge set is again given by (1.1).

As noted, there is an important element of uncertainty in a KPD program in that a selected exchange may not lead to a completed transplant due to the unavailability of the donor or the candidate, or because presumed compatibility is overturned by a laboratory crossmatch. Let $q_i \in [0, 1]$ denote the probability that both the donor and candidate of pair $i \in V^P$ are available through to transplantation. Similarly, for NDDs, let q_i denote the probability that NDD $i \in V^A$ remain available. For $e = (i, j) \in E$, let $p_e \equiv p_{ij} \in [0, 1]$ denote the probability of the match proving to be viable for transplantation. We assume that the success or failure of any given pair or NDD is independent of the success or failure of any other pair or NDD, and that match failures, conditional on the availability of the pairs or NDD involved, are

independent of each other as well.

Finally, we let the utility of $e = (i, j) \in E$ be given by $u_e \equiv u_{ij} \in \mathbb{R}^+$, as before. While it is common to assume a default utility of 1 for all matches, such that all potential transplants are valued equally, a more general utility assignment can account for various factors that would increase the priority of a transplant, such as the amount of time the matched candidate has been waiting in the KPD program, for example.

2.2.1 Locally Relevant Subgraphs

Recall that in the formulation described in Section 1.2, cycles and chains are represented as subgraphs of the original KPD network G. In general, any transplant arrangement of interest can be represented as a subgraph $S = (V_S, E_S)$ of G such that $V_S = V_S^P \cup V_S^A \subseteq V$, where $V_S^P \subseteq V^P$, $V_S^A \subseteq V^A$, and $E_S \subseteq \{(i, j) \in E \mid i, j \in V_S\}$. The arguments in this section are applicable to any class of transplant arrangements, including the class of cycles and chains, which simply restricts the edge sets to include only those matches directly involved in the cycle or chain.

Here, we describe a class of transplant arrangements that extend beyond simple cycles and chains, allowing for additional fallback options in cases of donor, candidate, or match failure. Wang et al. (2018) characterize the subgraphs of interest, based on an idea proposed by Li (2012) to identify strongly connected components of the underlying KPD compatibility graph. For fixed integer values of x, y, and L, where $\max(x, y) \leq L$, we consider subgraphs S of size $|V_S| \leq L$, where each vertex is involved in at least one sub-cycle of size at most x, or at least one sub-chain of length at most y. In addition, we require vertices within these subgraphs to be connected in such a way that any partition of the vertex set into two non-empty parts will result in the loss of at least one sub-cycle of size at most

x or sub-chain of length at most y. We refer to these subgraphs as Locally Relevant Subgraphs (LRS), and denote the class of all such subgraphs of G as $LRS(G; x, y, L)$.

The idea behind the LRS is that for a KPD network, it is easier to evaluate many smaller subgraphs in a divide-and-conquer manner than the single large network as a whole. A LRS consists of a size-restricted set of overlapping sub-cycles and sub-chains, allowing for additional fallback options to be considered after selection. As detailed earlier, we operate under the assumption that by selecting a LRS to evaluate for transplantation, once the availability of donors and candidates and viability of matches are confirmed, one would proceed to transplantation with the optimal set of remaining sub-cycles and sub-chains.

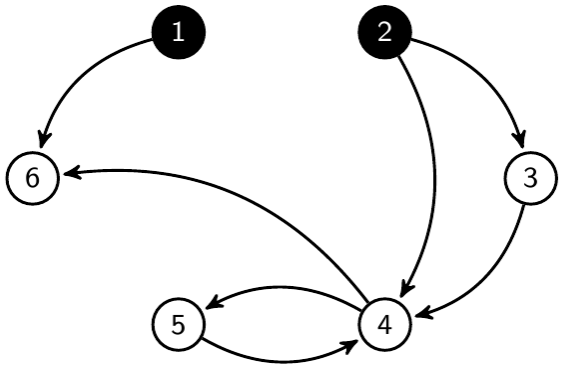


Figure 2.2: Example of a LRS of size 6 made up of two NDDs $V^A = \{1, 2\}$ (in black), and four incompatible donor-candidate pairs $V^P = \{3, 4, 5, 6\}$ (in white).

As an illustration, Figure 2.2 depicts an example of a LRS of size 6 made up of two NDDs, $V_S^A = \{1, 2\}$, represented by black vertices, and four incompatible donor-candidate pairs, $V_S^P = \{3, 4, 5, 6\}$, represented by white vertices. The LRS is denoted $S = (V_S, E_S)$, where $V_S = V_S^A \cup V_S^P = \{1, 2, 3, 4, 5, 6\}$, and $E_S = \{(1, 6), (2, 3), (2, 4), (3, 4), (4, 5), (4, 6), (5, 4)\}$. Letting $x = 3$ and $y = 3$, we have that, along with a single sub-cycle $c = \langle 4, 5 \rangle$, S consists of 8 sub-chains:

$c'_1 = \langle 1, 6\rangle$, $c'_2 = \langle 2, 3\rangle$, $c'_3 = \langle 2, 3, 4\rangle$, $c'_4 = \langle 2, 3, 4, 5\rangle$, $c'_5 = \langle 2, 3, 4, 6\rangle$, $c'_6 = \langle 2, 4\rangle$, $c'_7 = \langle 2, 4, 5\rangle$, $c'_8 = \langle 2, 4, 6\rangle$. Note that all pairs and NDDs in S can participate in a sub-cycle of size 3 or less, or a sub-chain of length 3 or less, and that S is connected such that any partition of the vertex set into two parts will result in the loss of a valid sub-cycle or sub-chain, defining features that characterize S as a suitable LRS.

LRSs as a class of transplant arrangements are more thoroughly examined in Wang et al. (2018), where methods of enumeration are also described.

2.2.2 Optimization with Locally Relevant Subgraphs

The optimization problem of interest can be written in a similar manner as (1.2). For $S \in LRS(G; x, y, L)$, let EU_S represent the expected utility of S. Subsequent sections will focus on the calculation of EU_S for all $S \in LRS(G; x, y, L)$ under the probability model defined previously, as necessary input to the optimization problem.

For each vertex $i \in V$, let $LRS_{(i)} = \{S \in LRS(G; x, y, L) : i \in V_S\} \subseteq LRS(G; x, y, L)$, the set of all LRSs in $LRS(G; x, y, L)$ that involve vertex i. Define a decision variable Y_S, with $Y_S = 1$ if $S \in LRS(G; x, y, L)$ is selected, and $Y_S = 0$ otherwise. The problem of selecting the optimal set of disjoint LRSs in G can then be formulated as the following IP problem:

$$\begin{aligned} &\max_{\{Y_S\}} \sum_{S \in LRS(G;x,y,L)} Y_S EU_S \\ &\text{subject to} \sum_{S \in LRS_{(i)}} Y_S \leq 1, \forall\ i \in V, \\ &Y_S \in \{0, 1\}, \forall\ S \in LRS(G; x, y, L). \end{aligned} \tag{2.1}$$

Thus, our aim is to select disjoint LRSs in $LRS(G; x, y, L)$ so as to maximize the total expected utility. The restrictions are such that no pair or NDD can appear in

more than one LRS. As in the traditional formulation, the problem, though possibly computationally extensive, can be solved with the aid of IP software such as Gurobi (Gurobi Optimization Inc.).

All sub-cycles and sub-chains contained within S, along with all disjoint combinations thereof, comprise the set of potential solutions, $\mathcal{C}_S^*$, to S. Assuming reasonable size constraints on the LRS, potential solutions can be determined by systematically examining each possible combination of sub-cycles and sub-chains, eliminating those with overlapping vertex sets. We note that, with the increase in uncertainty as the size of sub-cycles and sub-chains grows, we constrain sub-cycles and sub-chains to relatively small sizes and lengths, typically at most 3 in each case (such that $x = y = 3$).

We let potential solution $C^* = (V_{C^*}, E_{C^*}) \in \mathcal{C}_S^*$, be represented in graph notation, where the vertex set V_{C^*} and edge set E_{C^*} are the unions of the vertex and edge sets of its constituent sub-cycles and sub-chains. The utility of C^* is given by $U_{C^*} = \sum_{c \in C^*} U_c = \sum_{e \in E_{C^*}} u_e$, the sum of the utilities of the sub-cycles and sub-chains involved in that potential solution.

After confirming availability of donors and candidates and viability of transplants in a selected LRS S, we obtain $\bar{S} = (V_{\bar{S}}, E_{\bar{S}})$, the so-called observed subgraph of S, where $V_{\bar{S}} \subseteq V_S$ and $E_{\bar{S}} \subseteq \{e \equiv (i,j) \in E_S : i, j \in V_{\bar{S}}\}$. The set of potential solutions that remain in $\bar{S}$ is then given by $\mathcal{C}_{\bar{S}}^* \subseteq \mathcal{C}_S^*$. Transplants are ultimately realized from the set of disjoint sub-cycles and sub-chains $C_{\bar{S}}^* \in \mathcal{C}_{\bar{S}}^*$ that maximizes the utility. Let $\mathcal{C}_{\bar{S}}$ be the set of all sub-cycles and sub-chains remaining in $\bar{S}$, with $c = (V_c, E_c) \in \mathcal{C}_{\bar{S}}$ having an associated utility of $U_c = \sum_{e \in E_c} u_e$. $C_{\bar{S}}^*$ can be formally obtained as the solution to an IP problem similar to (2.1), in which $LRS(G; x, y, L)$ is replaced with $\mathcal{C}_{\bar{S}}$, S is replaced with c, and EU_S is replaced with U_c.

Returning to our example LRS depicted in Figure 2.2, assuming an equal utility of 1 for each match, the total utilities of each of the 9 sub-cycles and sub-chains are listed in Table 2.1. The remaining potential solutions, of which there are 8, arise from disjoint combinations of these sub-cycles and sub-chains, and are listed in Table 2.2 in set notation. In total, there are 18 possible solutions that can result from this LRS, including the situation where no transplants are ultimately possible.

Table 2.1: Sub-cycles and sub-chains for example LRS depicted in Figure 2.2.

Cycle/Chain	Utility
$c = \langle 4, 5 \rangle$	2
$c'_1 = \langle 1, 6 \rangle$	1
$c'_2 = \langle 2, 3 \rangle$	1
$c'_3 = \langle 2, 3, 4 \rangle$	2
$c'_4 = \langle 2, 3, 4, 5 \rangle$	3
$c'_5 = \langle 2, 3, 4, 6 \rangle$	3
$c'_6 = \langle 2, 4 \rangle$	1
$c'_7 = \langle 2, 4, 5 \rangle$	2
$c'_8 = \langle 2, 4, 6 \rangle$	3

Table 2.2: Potential solutions involving combinations of sub-cycles and sub-chains for LRS depicted in Figure 2.2.

Potential Solution	Utility
$\{c'_1, c'_2, c\}$	4
$\{c'_1, c'_4\}$	4
$\{c'_1, c'_3\}$	3
$\{c'_1, c'_7\}$	3
$\{c'_1, c'_8\}$	3
$\{c'_1, c\}$	3
$\{c'_2, c_1\}$	3
$\{c'_1, c'_2\}$	2

The potential solutions in Table 2.2 are arranged in non-increasing order of their utilities. The first two of these potential solutions represent ideal scenarios where all four candidates in the LRS receive a transplant. For viable solutions that are tied in utility, a secondary criterion can be added in order to determine their precedence.

2.3 Calculation of Expected Utilities for Locally Relevant Subgraphs

In this section, we describe methods for assigning an appropriate EU_S value for a given subgraph $S \in LRS(G; x, y, L)$.

2.3.1 Exact Calculation by Subgraph Enumeration

The crux of the exact calculation for expected utility hinges on considering every possible observed subgraph within S and determining its maximum utility as described in the previous section. Then, EU_S is obtained by multiplying the probability of observing each subgraph by its maximum utility, and taking the sum over all possible observed subgraphs.

Consider vertex subset $\bar{V} \subseteq V_S$. The probability that only the pairs and NDDs represented by $\bar{V}$ remain available for transplantation is given by

$$P(\bar{V}) = \prod_{i \in \bar{V}} q_i \prod_{i \in V_S / \bar{V}} (1 - q_i). \tag{2.2}$$

Let $S_{\bar{V}} = (\bar{V}, E_{\bar{V}})$ denote the subgraph induced by $\bar{V}$, where the edge set $E_{\bar{V}}$ is given by $E_{\bar{V}} = \{e = (i, j) \in E_S : i, j \in \bar{V}\}$. Now consider edge subset $\bar{E} \subseteq E_{\bar{V}}$. The probability that only the matches represented by $\bar{E}$ remain viable for transplantation is given by

$$P(\bar{E}|\bar{V}) = \prod_{e \in \bar{E}} p_e \prod_{e \in E_{\bar{V}} / \bar{E}} (1 - p_e). \tag{2.3}$$

With $\bar{S} = (\bar{V}, \bar{E})$ representing the observed subgraph of S, its solution $C^*_{\bar{S}}$ can be obtained as the solution to the IP problem (2.1). For subgraphs with reasonable size constraints, this solution may be deduced by simple inspection. The utility associated with $C^*_{\bar{S}}$ is given by $U_{C^*_{\bar{S}}} = \sum_{c \in C^*_{\bar{S}}} U_c = \sum_{e \in E_{C^*_{\bar{S}}}} u_e$. The expected utility EU_S of S is then obtained by taking the sum of all of the individual utilities for each possible observed subgraph, multiplied by the probability of that subgraph being

observed. That is,

$$EU_S = \sum_{\bar{V} \subseteq V_S} \sum_{\bar{E} \subseteq E_{\bar{V}}} P(\bar{V}) P(\bar{E}|\bar{V}) U_{C^*_{\bar{S}}} = \sum_{\bar{V} \subseteq V_S} P(\bar{V}) \sum_{\bar{E} \subseteq E_{\bar{V}}} P(\bar{E}|\bar{V}) U_{C^*_{\bar{S}}}. \tag{2.4}$$

We illustrate the steps to calculate the expected utility for the LRS depicted in Figure 2.3, made up of a single NDD $V^A = \{1\}$ and three incompatible donor-candidate pairs $V^P = \{2, 3, 4\}$. There are three possible sub-chains, denoted by $c'_1 = \langle 1, 2 \rangle$, $c'_2 = \langle 1, 2, 3 \rangle$, $c'_3 = \langle 1, 2, 3, 4 \rangle$, and one possible sub-cycle, denoted by $c = \langle 2, 3, 4 \rangle$. Table 2.3 summarizes the possible observed subgraphs alongside calculations required for each such subgraph with at least one remaining viable sub-cycle or sub-chain. Recall that we denote the probability of success of $e = (i, j) \in \bar{E}, i, j \in \bar{V}$ and its utility by $p_e \equiv p_{ij}$ and $u_e \equiv u_{ij}$ respectively. The expected utility is obtained by multiplying the values in the $P(\bar{V})$, $P(\bar{E}|\bar{V})$, and $U_{C^*_{\bar{S}}}$ columns in each row of Table 2.3, and then taking the sum across all of the rows.

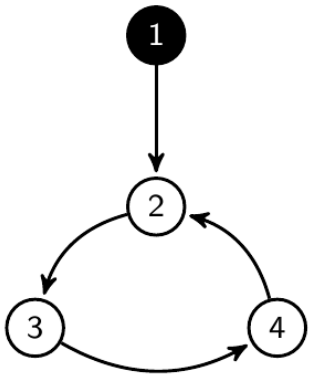


Figure 2.3: Example of a LRS of size 4 made up of a single NDD $V^A = \{1\}$ (in black), and three incompatible donor-candidate pairs $V^P = \{2, 3, 4\}$ (in white).

In a setting where a KPD program is restricted to selecting only cycles or chains, without recourse to fallback options, the previous calculations can be simplified. For cycles, if any of the pairs involved are unable to proceed to transplantation, or any of the matches are proven non-viable after a laboratory crossmatch, the cycle cannot

Table 2.3: Exact expected utility calculation by subgraph enumeration for LRS depicted in Figure 2.3.

$\bar{S}$	$\bar{V}$	$P(\bar{V})$	$\bar{E}$	$P(\bar{E}\|\bar{V})$	$C^*_{\bar{S}}$	$U_{C^*_{\bar{S}}}$
$\bar{S}_1$	$\{1,2\}$	$q_1q_2(1-q_3)\times(1-q_4)$	$\{(1,2)\}$	p_{12}	c'_1	u_{12}
$\bar{S}_2$	$\{1,2,3\}$	$q_1q_2q_3(1-q_4)$	$\{(1,2)\}$	$p_{12}(1-p_{23})$	c'_1	u_{12}
$\bar{S}_3$	$\vdots$	$\vdots$	$\{(1,2),(2,3)\}$	$p_{12}p_{23}$	c'_2	$u_{12}+u_{23}$
$\bar{S}_4$	$\{1,2,4\}$	$q_1q_2(1-q_3)q_4$	$\{(1,2)\}$	$p_{12}(1-p_{42})$	c'_1	u_{12}
$\bar{S}_5$	$\vdots$	$\vdots$	$\{(1,2),(4,2)\}$	$p_{12}p_{42}$	c'_1	u_{12}
$\bar{S}_6$	$\{2,3,4\}$	$(1-q_1)q_2q_3q_4$	$\{(2,3),(3,4),(4,2)\}$	$p_{23}p_{34}p_{42}$	c	$u_{23}+u_{34}+u_{42}$
$\bar{S}_7$	$\{1,2,3,4\}$	$q_1q_2q_3q_4$	$\{(1,2)\}$	$p_{12}(1-p_{23})\times(1-p_{34})(1-p_{42})$	c'_1	u_{12}
$\bar{S}_8$	$\vdots$	$\vdots$	$\{(1,2),(2,3)\}$	$p_{12}p_{23}(1-p_{34})(1-p_{42})$	c'_2	$u_{12}+u_{23}$
$\bar{S}_9$	$\vdots$	$\vdots$	$\{(1,2),(3,4)\}$	$p_{12}(1-p_{23})p_{34}(1-p_{42})$	c'_1	u_{12}
$\bar{S}_{10}$	$\vdots$	$\vdots$	$\{(1,2),(4,2)\}$	$p_{12}(1-p_{23})(1-p_{34})p_{42}$	c'_1	u_{12}
$\bar{S}_{11}$	$\vdots$	$\vdots$	$\{(1,2),(2,3),(3,4)\}$	$p_{12}p_{23}p_{34}(1-p_{42})$	c'_3	$u_{12}+u_{23}+u_{34}$
$\bar{S}_{12}$	$\vdots$	$\vdots$	$\{(1,2),(2,3),(4,2)\}$	$p_{12}p_{23}(1-p_{34})p_{42}$	c'_2	$u_{12}+u_{23}$
$\bar{S}_{13}$	$\vdots$	$\vdots$	$\{(1,2),(3,4),(4,2)\}$	$p_{12}(1-p_{23})p_{34}p_{42}$	c'_1	u_{12}
$\bar{S}_{14}$	$\vdots$	$\vdots$	$\{(2,3),(3,4),(4,2)\}$	$(1-p_{12})p_{23}p_{34}p_{42}$	c	$u_{23}+u_{34}+u_{42}$
$\bar{S}_{15}$	$\vdots$	$\vdots$	$\{(1,2),(2,3),(3,4),(4,2)\}$	$p_{12}p_{23}p_{34}p_{42}$	c or c'_3	$\max\{u_{12}+u_{23}+u_{34}, u_{23}+u_{34}+u_{42}\}$

proceed. Let $c = \langle i_1, \ldots, i_\ell \rangle$ be a cycle of size ℓ. Denote $e_1 = (i_\ell, i_1)$, and for $k = 2, \ldots, \ell$, let $e_k = (i_{k-1}, i_k)$. Finally, for $k = 1, \ldots, \ell$, let p_{e_k} and q_{i_k} denote the probability of success of e_k and of pair i_k, respectively, and let $U_c = \sum_{k=1}^{\ell} u_{e_k}$ be the utility of the cycle. The expected utility of c is given by:

$$EU_c = \left(\prod_{k=1}^{\ell} q_{i_k} p_{e_k} \right) U_c. \tag{2.5}$$

In some transplant centers, it may be administratively permissible for chains to be transplanted up to the first point of failure. As such, an appropriate expected utility calculation for chains in this setting would take into account direct sub-chains of the original chain as fallback options. Consider a chain $c' = \langle i_0, i_1, \cdots, i_\ell \rangle$ of length ℓ, with $e_k = (i_{k-1}, i_k)$ for $k = 1, \ldots, \ell$. Let $u'_k = \sum_{t=1}^{k} u_{e_t}$ be the utility of transplanting up to the candidate of pair i_k. The utility of the complete chain is given by $U_{c'} = u'_\ell = \sum_{t=1}^{\ell} u_{e_t}$. The expected utility calculation for chains in this context, adapted from Dickerson et al. (2013), is given by:

$$EU_{c'} = q_{i_0} \left\{ \sum_{k=1}^{\ell-1} (1 - q_{i_{k+1}} p_{e_{k+1}}) \left(\prod_{t=1}^{k} q_{i_t} p_{e_t} \right) u'_k + \left(\prod_{k=1}^{\ell} q_{i_k} p_{e_k} \right) U_{c'} \right\}. \tag{2.6}$$

The first summand accounts for situations where the chain reaches the candidate of pair i_k for $k \in \{1, \ldots, \ell-1\}$, with failure occurring in the transplant to the candidate of pair i_{k+1}. The second summand accounts for the complete chain being realized.

2.3.2 Exact Calculation by Inclusion-Exclusion

While intuitive, the method in Section 2.3.1 requires searching through every possible vertex-edge subset within each LRS under review. As there are $2^{|V_S|}$ possible vertex subsets within S, where each vertex subset $\bar{V}$ induces a subgraph which itself has $2^{|E_{\bar{V}}|}$ possible edge subsets, computations can quickly become prohibitive for even moderately-sized LRSs. Fortunately, due to the restricted size of the LRS, enumerating the sub-cycles and sub-chains within a LRS and determining the potential solutions within is straightforward. Here, we use the principle of inclusion-exclusion to calculate the probabilities that each potential solution will be realized as the best option for transplantation, which can then be used to calculate the expected utility of the LRS.

Suppose S is a LRS with $|\mathcal{C}_S^*| = K$ potential solutions, denoted $C_1^*, C_2^*, \ldots, C_K^*$. Without loss of generality, we suppose that these potential solutions have been arranged in non-increasing order of their utilities, such that $U_{C_1^*} \geq U_{C_2^*} \geq \cdots \geq U_{C_K^*}$.

We represent $C_k^* = (V_{C_k^*}, E_{C_k^*})$ in graph notation. With a slight abuse of notation, we also let C_k^* represent the event that potential solution C_k^* is viable. This is the case when all pairs and matches involved in the solution prove to be viable, so that

$$P(C_k^*) = \prod_{i \in V_{C_k^*}} q_i \prod_{e \in E_{C_k^*}} p_e. \tag{2.7}$$

Further, the joint event that two potential solutions $C_{k_1}^*$ and $C_{k_2}^*$ are simultaneously viable, denoted here by $C_{k_1}^* C_{k_2}^*$, $k_1, k_2 \in \{1, \ldots, K\}$, $k_1 < k_2$, can be identified similarly based on whether every distinctive vertex and edge involved in either of the two options is viable. In other words, the vertex set and edge set are given by $V_{C_{k_1}^*} \cup V_{C_{k_2}^*}$ and $E_{C_{k_1}^*} \cup E_{C_{k_2}^*}$, respectively, and it follows that

$$P(C_{k_1}^* C_{k_2}^*) = \prod_{i \in V_{C_{k_1}^*} \cup V_{C_{k_2}^*}} q_i \prod_{e \in E_{C_{k_1}^*} \cup E_{C_{k_2}^*}} p_e. \tag{2.8}$$

The joint probabilities of any $3, 4, \ldots, K$ potential solutions being simultaneously viable can all be determined in a similar manner.

For $k = 1, \ldots, K$, we denote by P_k the probability that the potential solution C_k^* will be selected as the optimal solution for S. It follows that $P_1 = P(C_1^*)$, as the probability that the best potential solution is selected depends only on whether or not it is viable. For $k = 2, \ldots, K$, C_k^* will be only be preferentially selected if it remains viable, and those potential solutions $C_{k'}^*$, $k' = 1, \ldots, k-1$, with higher precedence according to utility are found to no longer be viable. Thus, denoting the difference between two arbitrary sets A and B by $A - B = \{x \in A : x \notin B\}$, we have that $P_k = P\left(C_k^* - \bigcup_{t=1}^{k-1} C_t^*\right)$, and applying the idea of inclusion-exclusion, we obtain:

$$
\begin{aligned}
P_k &= P\left(C_k^* - \bigcup_{t=1}^{k-1} C_t^*\right) \\
&= P\left(C_k^*\right) - P\left(C_k^* \cap \left(C_1^* \cup C_2^* \cup \cdots \cup C_{k-1}^*\right)\right) \\
&= P\left(C_k^*\right) - \sum_{t=1}^{k-1} P(C_t^* C_k^*) + \sum_{\substack{t_1,t_2 \in \{1,\ldots,k-1\} \\ t_1 > t_2}} P(C_{t_1}^* C_{t_2}^* C_k^*) \pm \ldots (-1)^{k-1} P\left(C_1^* \cdots C_k^*\right),
\end{aligned}
\tag{2.9}
$$

where each individual probability term can be calculated as described above in (2.7) and (2.8). The expected utility is then given by

$$
EU_S = \sum_{k=1}^{K} P_k U_{C_k^*}. \tag{2.10}
$$

Returning to our previously worked example from Section 2.3.1, suppose we prefer transplanting the sub-cycle c over the long sub-chain c_3' (i.e. $u_{42} > u_{12}$). Our potential solutions, in order, are then given by $C_1^* = c$, $C_2^* = c_3'$, $C_3^* = c_2'$, $C_4^* = c_1'$, with $U_{C_1^*} = u_{23} + u_{34} + u_{42}$, $U_{C_2^*} = u_{12} + u_{23} + u_{34}$, $U_{C_3^*} = u_{12} + u_{23}$, and $U_{C_4^*} = u_{12}$. Using inclusion-exclusion as in (2.9), the probability of each solution being selected is given as follows:

1. For C_1^*, $P_1 = P(C_1^*)$
2. For C_2^*, $P_2 = P(C_2^*) - P(C_1^* C_2^*)$
3. For C_3^*, $P_3 = P(C_3^*) - P(C_1^* C_3^*) - P(C_2^* C_3^*) + P(C_1^* C_2^* C_3^*)$
4. For C_4^*,

   $P_4 = P(C_4^*) - \sum_{t=1}^{3} P(C_t^* C_4^*) + \sum_{\substack{t_1,t_2 \in \{1,2,3\} \\ t_1 > t_2}} P(C_{t_1}^* C_{t_2}^* C_4^*) - P(C_1^* C_2^* C_3^* C_4^*)$

The values of each of the individual probability terms are calculated as in (2.7) and (2.8). For example, $P(C_1^*)$, the probability of the sub-cycle $c = \langle 2, 3, 4 \rangle$ being viable, is given by $q_2 q_3 q_4 p_{23} p_{34} p_{42}$, while $P(C_4^*)$, the probability of the smallest sub-chain $c_3' = \langle 1, 2 \rangle$ being viable is given by $q_1 q_2 p_{12}$. The probability of both of these

options remaining viable is effectively the probability of every pair, NDD and match in the LRS remaining viable, such that $P(C_1^* C_4^*) = q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34} p_{42}$.

Using inclusion-exclusion in this manner is preferable to the subgraph enumeration method from Section 2.3.1 when the number of potential solutions is small relative to the number of possible observed subgraphs, as we avoid having to calculate the probability and utility of every possible vertex-edge subset of the original LRS, many of which will have no remaining sub-cycles or sub-chains and thus will not contribute to the expected utility calculation.

2.3.3 Matrix Formulation

We can formulate a matrix implementation to simplify the expected utility computations. Suppose S is a LRS with K potential solutions, denoted by $C_1^*, C_2^*, \ldots, C_K^*$, again ordered such that $U_{C_1^*} \geq U_{C_2^*} \geq \cdots \geq U_{C_K^*}$. As a convention, we will let $C_0^* = \emptyset$, where no solution is viable, with $U_{C_0^*} = 0$. Also, let H denote the number of possible observed subgraphs of S.

We construct matrices $\mathbf{A}$ and $\mathbf{B}$, representing the subgraphs and the potential solutions of S respectively, as follows. Let the h-th subgraph $S_h = (V_h, E_h)$ be an observable subgraph of S. The probability of observing the subgraph S_h is:

$$P(S_h) = \prod_{i \in V_h} q_i \prod_{i \in V_S / V_h} (1 - q_i) \prod_{e \in E_h} p_e \prod_{e \in E_{V_h} / E_h} (1 - p_e). \tag{2.11}$$

Suppose the vertices in V_S and edges in E_S are numbered $1, \ldots, |V_S|$ and $|V_S| + 1, \ldots, |S|$, respectively, where $|S| = |V_S| + |E_S|$. Denote a vector of binary variables by $A_h = [a_{1h}\ a_{2h}\ \ldots\ a_{|S|h}]^T \in \{0,1\}^{|S|}$, where the h-th element is given by

$$a_{ih} = \begin{cases} \mathbb{1}\left(i \in V_h\right), & 1 \leq i \leq |V_S| \\ \mathbb{1}\left(i \in E_h\right), & |V_S| + 1 \leq i \leq |S|. \end{cases} \tag{2.12}$$

Each vector A_h characterizes a subgraph by both its vertices and edges. Let $\mathbf{A} = [A_1, \ldots, A_H]$, the $|S| \times H$ matrix of all possible valid subgraphs within the LRS. Similarly, let $\mathbf{B} = (b_{ik})$ be the $|S| \times K$ matrix characterizing the potential solutions of S, constructed analogously to $\mathbf{A}$, where the (i,k)-th element is given by

$$b_{ik} = \begin{cases} \mathbb{1}\left(i \in V_{C_k^*}\right), & 1 \leq i \leq |V_S| \\ \mathbb{1}\left(i \in E_{C_k^*}\right), & |V_S| + 1 \leq i \leq |S|. \end{cases} \tag{2.13}$$

Let $\mathbf{W} = \mathbf{B}^T\mathbf{A}$, where w_{kh} gives the number of vertices and edges in common between the k-th potential solution and the h-th observable subgraph. Also, let $\mathbf{t} = \mathbf{B}^T\mathbf{1}$, where $\mathbf{1}$ is a vector of ones. The elements t_k of $\mathbf{t}$ correspond to the total number of vertices and edges, or pairs/NDDs and matches, involved in the potential solution. For each $h = 1, \ldots, H$, let

$$k_h = \begin{cases} \min\{k \in 1, \ldots, K : t_k = w_{kh}\} & \text{if } \exists\ k \in 1, \ldots, K \text{ st. } t_k = w_{kh} \\ 0 & \text{o.w.,} \end{cases} \tag{2.14}$$

be the preferred potential solution for the corresponding subgraph. The expected utility is then given by

$$EU_S = \sum_{h=1}^{H} U_{C_{k_h}^*} P(S_h). \tag{2.15}$$

In this manner, some redundant calculations are avoided when comparing to the method described in Section 2.3.1. We require the list of potential solutions be pre-specified, as in 2.3.2.

2.3.4 Estimation by Monte Carlo Sampling

Exact calculations described in the previous sections can become computationally prohibitive as the size of the LRSs under consideration, and thus the number of fallback options, is allowed to increase. The LRS in Figure 2.2, for example, has 370

observable subgraphs and 18 potential solutions. The inclusion-exclusion procedure would then involve calculating up to 2^{17} probability terms. Enumerating the possible observed subgraphs and determining the optimal potential solution as in Section 2.3.3 is an improvement, but still involves a significant amount of calculation. In such cases, it may be preferable, or even necessary, to approximate the expected utility to be used in place of an exact expected utility.

Due to the presumed independence between pair failures, as well as match failures conditional on the availability of the pairs, a simple Monte Carlo sampling procedure can be used to obtain an appropriate expected utility. For a given LRS, we separately sample whether each pair or NDD succeeds, followed by whether each match between successful pairs and NDDs succeeds. This yields a sampled observed subgraph, the utility of which can be determined by a maximum utility selection among its sub-cycles and sub-chains, as in Section 2.3.1. By determining all potential solutions and their precedence within the LRS beforehand, we can also instead compare the sampled subgraph to the potential solutions $C_1^*, C_2^*, \ldots, C_K^*$ in sequence, recording the utility of the first of these potential solutions that remains viable. Repeating either of these procedures for a large number of iterations, one then assigns to the LRS an expected utility given by the average of the utilities of the sampled subgraphs.

This sampling procedure can be implemented using matrix multiplication as in Section 2.3.3. Consider sampled subgraphs $S_n = (V_n, E_n), n = 1, \ldots, N$, where N is the number of sampled subgraphs, and let $\tilde{A}_n = [\tilde{a}_{1n}\ \tilde{a}_{2n}\ \cdots\ \tilde{a}_{|S|n}]^T$ be a vector of binary variables similar to that shown in (2.12), where in this case,

$$\tilde{a}_{in} = \begin{cases} \mathbb{1}(i \in V_n), & 1 \leq i \leq |V_S| \\ \mathbb{1}(i \in E_n), & |V_S| + 1 \leq i \leq |S|. \end{cases} \tag{2.16}$$

Let $\tilde{\mathbf{A}} = \left[\tilde{A}_1, \cdots, \tilde{A}_N\right]$, the $|S| \times N$ matrix of sampled subgraphs (note that this matrix is not the same as $\mathbf{A}$ from Section 2.3.3). Let $\mathbf{B}$ be the same as described by (2.13) in Section 2.3.3, and $\mathbf{t} = \mathbf{B}^T\mathbf{1}$ as before. Let $\tilde{\mathbf{W}} = \mathbf{B}^T\tilde{\mathbf{A}}$, where $\tilde{w}_{kn}$ gives the number of vertices and edges, or pairs/NDDs and matches, in common between the k-th potential solution and the n-th sampled subgraph. For each $n = 1, \ldots, N$, let

$$k_n = \begin{cases} \min\{k \in 1, \ldots, K : t_k = \tilde{w}_{kn}\} & \text{if } \exists\ k \in 1, \ldots, K \text{ st. } t_k = \tilde{w}_{kn} \\ 0 & \text{o.w.} \end{cases} \tag{2.17}$$

be the optimal solution for the n-th sampled subgraph. The estimated expected utility is therefore given by

$$\widehat{EU}_S = \frac{1}{N}\sum_{n=1}^{N} U_{C^*_{k_n}}. \tag{2.18}$$

2.4 Comparison of Expected Utility Methods

We perform simulation experiments to evaluate the expected utility methods presented in Section 2.3. In the first experiment, Table 2.4 displays the running time needed to calculate or estimate the expected utility for LRSs of size 3, 4, and 5, comprised only of pairs in which every donor is found to match every other candidate. In other words, the underlying subgraph is complete. With the maximum sub-cycle size set to 3, the number of potential solutions is 5, 17, and 65, for subgraphs of size 3, 4, and 5 respectively. Note that the reported running times for the estimation method are based on 1000 Monte Carlo sample subgraphs of the LRS. The failure probability was set to 0.5 for all pairs, and to 0.2 for all matches.

From Table 2.4, it is clear that exact expected utility calculation becomes prohibitive as the size of the subgraph and the number of potential solutions increase. With complete graphs, even for a LRS of size 4, estimating the expected

Table 2.4: Time (in milliseconds) to determine expected utility for pairs-only complete subgraphs.

Expected Utility Method	3 Pairs	4 Pairs	5 Pairs
Subgraph Enumeration	1.00	182.21	4.42×10^6
Inclusion-Exclusion	0.16	1237.18	(Not Completed)
Monte Carlo Estimation (1000 Iterations)	1.34	2.53	4.85

utility is preferred over exact calculation. It should be noted, however, that observing a complete graph of large size would be uncommon in practice. These complete graph experiments correspond to the most computationally challenging worst-case scenarios.

In a second experiment, we generated LRSs comprised of exactly 5 pairs and consisting of either 9, 10, 11 or 12 matches. 10,000 LRSs of each specified number of matches were generated at random, and their expected utilities were calculated both by inclusion-exclusion and by estimation based on 1,000 Monte Carlo samples. Failure probabilities were the same as in the previous experiment. Figure 2.4 displays the expectation and standard error, stratified by number of matches and potential solutions, of the relative difference in expected utility values obtained by estimation $\widehat{EU}_S$, and exact calculation, EU_S, given by the difference in estimated and exact expected utilities, divided by the exact expected utility. Note that Figure 2.4 plots a random sample of 1,000 LRSs within each stratum comprising at least 1,000 generated LRSs. Also note that estimation precision will increase with the number of samples, as the standard error is of order $1/\sqrt{N}$, where N again represents the number of samples used to estimate the expected utility. In terms of runtime, for a given number of matches, the superiority of estimation relative to exact calculation increases as the number of potential solutions increases. Such experiments may be utilized to determine suitable thresholds at which to switch between estimating and calculating the expected utility in practice.

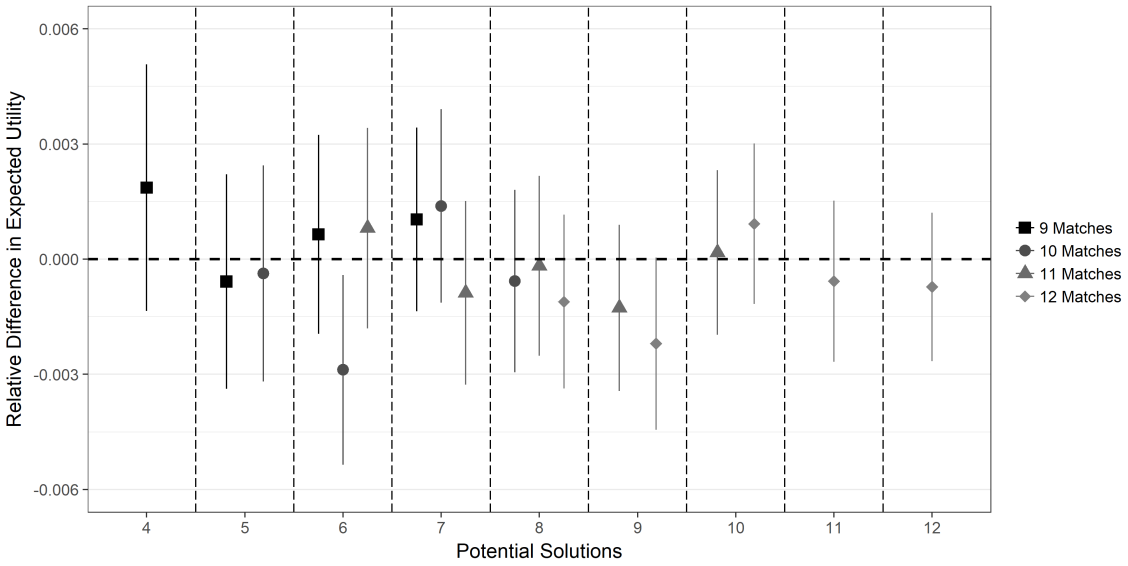


Figure 2.4: Relative difference in expected utility, split by number of potential solutions.

Finally, we compare solutions obtained by exact calculation and estimation of expected utility, using either 100 or 1000 iterations for estimation, for LRSs in a pool of 100 pairs (no NDDs). Candidate information is based on data from 380 incompatible donor-candidate pairs from the Alliance for Paired Donation. Each pair is generated by sampling a candidate with replacement, and by assigning a randomly-generated donor, where the blood type is sampled based on the marginal blood type probabilities in kidney transplant donors from the Scientific Registry of Transplant Recipients, and HLA information is sampled from the HLA profile frequencies from the Bone Marrow Transplant Registry (Maiers et al., 2007). If the donor generated through this procedure is found to be compatible with the selected candidate, we re-generate donor characteristics until an incompatible donor is obtained. LRSs are constrained to a maximum size of 4, with sub-cycles of maximum size 3.

Each donor is assessed for compatibility with all other candidates by virtual crossmatch, and the best LRS solution in terms of expected utility is produced. In order to introduce additional variability to the expected utility assignments,

instead of optimizing in terms of the number of transplants, we assign a utility value to each match from a continuous uniform distribution, $U(1, 10)$. All candidates are assumed to fail with probability 0.25, donors with probability 0.10, and matches with probability drawn from a continuous uniform distribution, $U(0, 0.25)$. For each estimated utility solution, we calculate the corresponding exact expected utility of the selected subgraphs. Simulations were written in C++, and optimal solutions were selected using the linear programming software Gurobi (Gurobi Optimization Inc.).

Across 50 such generated pools, the average relative difference between the exact expected utility solution and the true expected utility of the estimated utility solution, using 100 iterations per LRS, is 0.0104, corresponding to a roughly 1% loss in expected utility due to the approximation. For the estimated solution using 1000 iterations per LRS, this average relative difference drops to 0.0012, representing a roughly 0.1% loss in expected utility. Again, the ability to measure the accuracy of the approximation relative to the true expected utility can aid in choosing an appropriate number of iterations to employ in the estimation, given the number of matches or potential solutions within the LRS, for example.

2.5 Simulation

We evaluate several optimization settings with respect to the number of realized transplants and their characteristics over the course of several match runs in a realistic dynamic model of a KPD program, similar to that outlined in Ashlagi et al. (2011).

Here we use de-identified data on 538 donor-candidate pairs and 55 NDDs (including bridge donors) from the APD. The data set includes donor and

candidate blood type, HLA information for the donors, and unacceptable HLA information and panel reactive antibody (PRA) for the candidates. The PRA value represents the estimated percentage of donors to which the candidate is expected not to match in a typical pool of donors. Note that this value is an estimation, such that a candidate with a PRA of 0, for example, may not necessarily denote complete non-sensitization (Velidedeoglu et al., 2018). Using this information on donors and candidates, a virtual crossmatch is performed for every possible combination of donor and candidate, by assessing blood type and HLA compatibility.

For each match, we assign a probability that the transplant will turn out to be non-viable, which we base on the PRA of the candidate. These baseline probabilities are the same as in Ashlagi et al. (2011), who remark that they are empirically determined. For candidates with a PRA between 0 and 24, the baseline failure probability is 0.05; between 25 and 49, the probability is 0.2; between 50 and 74, the probability is 0.35; between 75 and 100, the probability is 0.5. Additional failure probabilities of 20% are added to these baseline values in a sensitivity analysis to reflect potentially higher probabilities of match failure due to candidate, donor or transplant center preferences. We also consider the probability that each selected pair would be unable to proceed to transplant, which we take to be 0% or 20% in our simulations.

We consider three optimization settings. The simplest setting, "Cycles and Chains", involves simply maximizing the utility of the selected cycles and chains, the standard approach in KPD. The second setting, "Cycles and Chains with Fallbacks", takes failure probabilities into account and aims to select the set of cycles and chains with the largest expected utility, under the assumption that

fallback options will be taken in cases of non-viability. The final setting, "Locally Relevant Subgraphs", implements our LRS approach, aiming to maximize the set of LRSs with the largest expected utility, given uncertainty and fallback options. Optimal solutions were again obtained using Gurobi (Gurobi Optimization Inc.).

Simulation parameters and conditions follow those in Ashlagi et al. (2011). Two hundred simulations of evolving KPD pools over 8 match runs are performed. At the beginning of each simulation, 30 incompatible pairs and 1 NDD for each of the 8 match runs are sampled with replacement from the APD dataset. We consider DPD chains, with implicit final donation to the deceased donor waitlist, with a maximum length of 2, as well as NEAD chain segments, where the final donor is retained as a bridge donor for future match runs, with maximum lengths of 3, 4 and 5. Each generated pool is evaluated under each of the different optimization settings and specified maximum chain lengths.

After selection, proposed transplants can fail to proceed, either due to positive lab crossmatch, based on the match failure probability, or if one of the pairs involved is unable to proceed to transplant, based on the pair failure probability. For all matches that remain, success probabilities are updated after evaluation, to 1 if successful and 0 otherwise, for use in future calculations. Following completion of each match run, each pair in the pool has a 2% chance of permanently leaving the pool prior to the next match run. Bridge donors have a renege rate of 1%, representing the rate at which they renege on their commitment to continue the chain after their associated recipient receives their transplant. Chains which would leave bridge donors with blood type AB are not considered in the simulation. NDDs and bridge donors remaining at the end of the final match run are recorded as giving rise to one additional transplant, reflecting their potential to provide

further transplants in future match runs.

Note that, due to computational complexity, the Cycles and Chains with Fallbacks scheme is only evaluated for chain segments of maximum length 4 in each match run. The Locally Relevant Subgraphs scheme considers LRSs of size 3 or less, restricting to sub-chains of maximum length 2, and those of size 4 or less, restricting to sub-chains of maximum length 3. For more details about the simulation, we refer the reader to Bray et al. (2015).

Figure 2.5 plots the ratio of the number of transplants achieved under each simulation setting, compared to the Cycles and Chains simulation with maximum chain length of 2. We observe that simply maximizing the number of transplants through cycles and chains, without taking into account the probabilities of failure or fallback options, delivers diminishing returns as chain segment length increases beyond 4. As compared to the simplest simulation setting, we obtain between 2% to 44% more transplants by using a fallback option approach with increasing allowance for longer chains. In general, the advantage of schemes with fallback options over the standard KPD approach increases as the failure probabilities increase. The Locally Relevant Subgraphs setting with maximum chain length of 3 outperformed all other schemes regardless of maximum chain length considered, providing the largest number of realized transplants in all simulations.

The distribution of blood types among transplant recipients is similar for all optimization, chain length, and failure probability settings. Similarly, we do not observe any differences between optimization settings in the proportion of candidates of each blood type receiving a transplant over the course of the match runs. It is interesting to note that an approach that only considers an expected utility based on failure probabilities, but without accounting for fallback options,

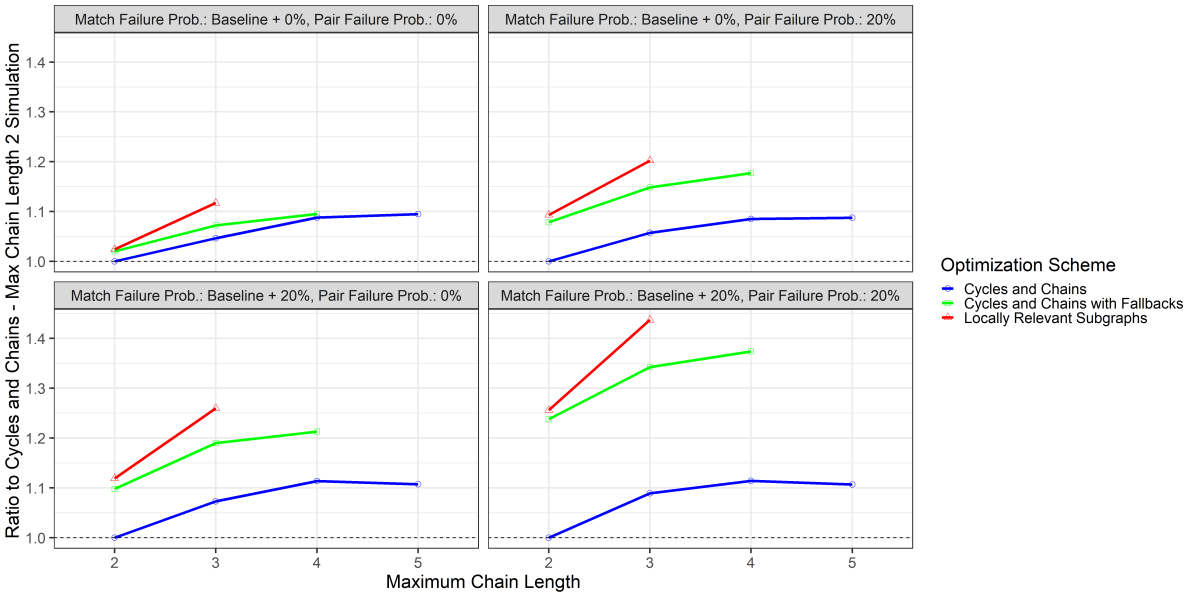


Figure 2.5: Ratio of number of realized transplants for each optimization scheme compared to the Cycles and Chains setting with maximum chain length of 2 (DPD), under various pair and match failure probability settings. Baseline match failures are assumed based on candidate PRA.

would be expected to introduce bias against higher PRA candidates for whom selected transplants are less likely to be completed. Taking account of fallback options at the optimization stage, however, greatly reduces these biases. It appears that incorporating fallback options in the optimization tends to allow for more candidates with high PRA in the selected solutions, since the penalty for their inclusion is reduced by accounting for the ability to take fallback options where possible.

2.6 Discussion

In this chapter, we detailed the calculation of expected utility for a more general class of transplant arrangements, the locally relevant subgraphs, in a KPD program, assuming the possibility of selected pairs or matches being unable to proceed to transplantation and the pursuit of fallback options in such cases. We described exact and sampling-based estimation methods for assigning expected utility values to such

arrangements. It is clear that solutions involving many fallback options should be preferred in a KPD program.

The issue of searching for relevant subgraphs within the KPD network, as well as for sub-cycles and sub-chains within these subgraphs, are themselves interesting problems. These operations can be computationally expensive, so procedures that streamline this process are beneficial in practice. The strategy of decomposing a large KPD network into a set of small cohesive subgraphs with high numbers of fallback options is desirable to make the proposed expected utility calculations useful and practically appealing. Algorithms for searching a KPD graph for relevant subgraphs have been studied in Wang et al. (2018).

A number of recent studies attempt to address the practical and computational bottlenecks in the KPD problem. Blum et al. (2015) propose pre-testing some small number of promising potential matches for a certain subset of patient-donor pairs in a KPD program, and show by simulation the expected effect on the number of realized exchanges. Pedroso (2014) assemble a database of possible configurations of subgraphs up to a given size, and store the function calculating the expected utility to be assigned along with each of the configurations. With appropriate data structures, it is computationally acceptable to search this database for a graph which is isomorphic to the subgraph under consideration. This idea of storing the types of subgraphs to be considered can further be extended to include NDDs (Alvelos et al., 2016). However, the size of the graphs in these cases are typically small, and their number is limited.

CHAPTER III

A Generalized Model for Kidney Paired Donation

3.1 Introduction

The standard formulation for KPD assumes that each transplant candidate joins the program with a single incompatible donor. However, it is possible for a transplant candidate to join KPD with more than one incompatible donor, with organ exchanges involving any one of these donors. Here, we extend and generalize the previously studied model for KPD, with the possibility of failure and the recourse to fallback options, to include candidates joining KPD with any number of incompatible donors. We also consider a state transition model for individual donor and candidate failures, where KPD participants alternate between active and inactive participation in the KPD program over time. Note that we will continue to use the term "pair", referring in this context to a transplant candidate and all of his or her associated incompatible donors.

3.2 Modeling Candidates with Multiple Incompatible Donors

To reflect the possibility of candidates joining KPD with more than one incompatible donor, we adapt the original KPD network $G = (V, E)$ to allow each individual vertex to have multiple edges to other vertices. In other words, we now consider G as a directed multigraph.

Let $V = V^P \cup V^A$ as before. Here we consider pair $v_i = (r_i, D_i) \in V^P$, where r_i represents the candidate (r stands for "recipient"), and $D_i = \{d_{i1}, ..., d_{iM_i}\}$ represents the set of $M_i \geq 1$ incompatible donors associated with candidate r_i. Note that for NDD $v_i \in V^A$, $D_i = \{d_{i1}\} \equiv d_i$. Let E_{ij} be the set of all matches between donors D_i of $v_i \in V$, and the candidate r_j of $v_j \in V^P$. That is, we have that

$$E_{ij} = \{e_{imj} \equiv (d_{im}, r_j) : m \in \{1, ..., M_i\}, v_i \in V, v_j \in V^P, i \neq j, \tag{3.1}$$

successful virtual crossmatch from donor m of v_i to candidate of $v_j\}$.

It follows that $E = \bigcup_{v_i \in V,\ v_j \in V^P,\ i \neq j} E_{ij}$.

Figure 3.1 gives an example of a LRS involving a multiple donor pair. The LRS has three pairs, where pair v_1 has two donors, such that $D_1 = \{d_{11}, d_{12}\}$. Pairs v_2 and v_3 each have a single donor, such that $D_2 = \{d_{21}\} \equiv d_2$ and $D_3 = \{d_{31}\} \equiv d_3$. There are three potential solutions in this LRS. Two sub-cycles of size 3 are possible between these pairs, with the first transplant to candidate r_2 coming either from donor d_{11} or d_{12}. Should either of these options prove to be non-viable, there is a fallback option, a sub-cycle of size 2 between pairs 1 and 3. However, this cycle is contingent on the availability of d_{11}, since d_{12} is not compatible with r_3, as is evident by the absence of a match e_{123}.

Again, we focus on the set of locally relevant subgraphs denoted by $LRS(G; x, y, L)$ for selection. For the purpose of determining appropriate LRSs to consider within our KPD network, we can reduce the multigraph G to a simple directed graph $G' = (V, E')$, by collapsing the multiple edges from one vertex to another into a single edge, such that $e = (i, j) \in E' \iff E_{ij} \neq \emptyset$. In this way, enumeration of LRSs proceeds as in Wang et al. (2018), and optimization proceeds as in (2.1). The following sections describe the derivation of the appropriate assignment of expected utility to assign to each LRS, given the additional fallback

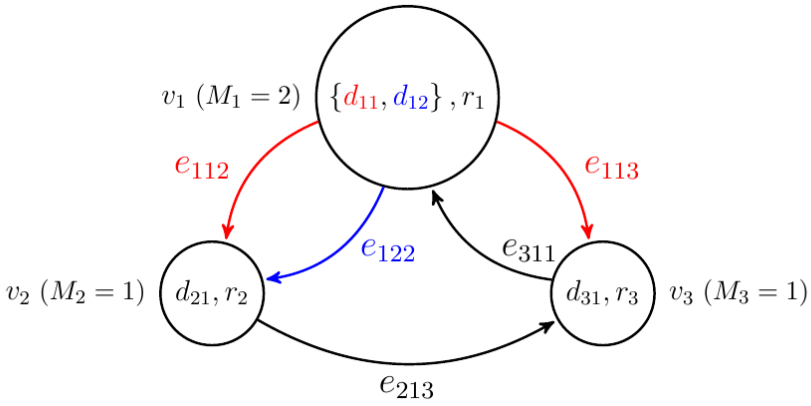


Figure 3.1: Illustration of a LRS involving three "pairs", the first of which (top) having two associated donors. For this pair, the portions of the LRS involving the first donor d_{11} are colored in red, while those involving the second donor d_{12} are colored in blue, for ease of differentiation.

options afforded by the multiple donors.

3.2.1 Calculation of Expected Utilities with Multiple-Donor Candidates

Let $u_{imj} \in \mathbb{R}^+$ represent the utility of the potential transplant from donor d_{im} to candidate r_j, and $p_{imj} \in [0, 1]$ its probability of success. The probabilities of being available through to transplantation associated with donor d_{im} and candidate r_i are denoted as q^d_{im} and q^r_i respectively.

The expected utility calculation follows a similar procedure as in Section 2.3.1. Here, the separation of probabilities of viability of the donors and the candidates induces an extra layer of subsetting in the subgraph enumeration. Let $S = (V_S, E_S) \in LRS(G; x, y, L)$ as before, and consider $R_S = \{r_i : v_i \in V_S\}$, the set of candidates in the LRS. Consider a subset of the candidates, denoted $\bar{R} \subseteq R_S$. The probability that this exact subset of candidates will be available at the transplantation stage is given by

$$P(\bar{R}) = \prod_{i \in V_S:\ r_i \in \bar{R}} q^r_i \prod_{i \in V_S:\ r_i \in R_S/\bar{R}} (1 - q^r_i)\,. \tag{3.2}$$

Conditional on this set of candidates being available, consider the set $D_{\bar{R}} = \{d_{im} :$

$v_i \in V_S, r_i \in \bar{R}, m \in \{1, \ldots, M_i\}\}$, which represents the set of all donors associated with these candidates. Now consider a subset of these donors, denoted $\bar{D} \subseteq D_{\bar{R}}$. The probability that this exact subset of donors will be available at the transplantation stage is given by

$$P(\bar{D}|\bar{R}) = \prod_{\{i,m\}:\ d_{im} \in \bar{D}} q^d_{im} \prod_{\{i,m\}:\ d_{im} \in D_{\bar{R}}/\bar{D}} \left(1 - q^d_{im}\right). \tag{3.3}$$

Finally, conditional on this set of candidates and donors being available, consider the set $E_{\bar{D},\bar{R}} = \{e_{imj} \in E_S : v_i, v_j \in V_S, i \neq j, m \in \{1, \ldots, M_i\}, r_j \in \bar{R}, d_{im} \in \bar{D}\}$, the remaining edges between donors from one pair to a candidate in another pair. The probability that an exact subset $\bar{E} \subseteq E_{\bar{D},\bar{R}}$ of matches will be deemed viable for transplantation is given by

$$P(\bar{E}|\bar{D}, \bar{R}) = \prod_{\{i,m,j\}:e_{imj} \in \bar{E}} p_{imj} \prod_{\{i,m,j\}:e_{imj} \in E_{\bar{D},\bar{R}}/\bar{E}} (1 - p_{imj}). \tag{3.4}$$

The sets $\bar{E}$, $\bar{D}$, and $\bar{R}$ characterize the observed subgraph $\bar{S} = (\bar{V}, \bar{E})$, where $\bar{V}$ can be reconstructed as $\bar{V} = \{v_i \in V : r_i \in \bar{R}, \exists\ m \in \{1, \ldots, M_i\}\ st.\ d_{im} \in \bar{D}\}$. $\mathcal{C}^*_{\bar{S}}$ then represents the optimal solution of sub-cycles and sub-chains within $\bar{S}$, as before, and we have that, $U_{\mathcal{C}^*_{\bar{S}}} = \sum_{c \in \mathcal{C}^*_{\bar{S}}} U_c$. Note that, for sub-cycles with more than one match from donors of a given pair to their assigned candidate, we select the donor contributing the largest utility.

The expected utility of S is obtained by taking the sum of all of the individual expected utilities for each observable donor-candidate-match subgraph, multiplied by the probability of that subgraph being observed. That is,

$$\begin{aligned} EU_S &= \sum_{\bar{R} \subseteq R_{\bar{S}}} \sum_{\bar{D} \subseteq D_{\bar{R}}} \sum_{\bar{E} \subseteq E_{\bar{D},\bar{R}}} P(\bar{R}) P(\bar{D}|\bar{R}) P(\bar{E}|\bar{D}, \bar{R}) U_{\mathcal{C}^*_{\bar{S}}} \\ &= \sum_{\bar{R} \subseteq R_{\bar{S}}} P(\bar{R}) \sum_{\bar{D} \subseteq D_{\bar{R}}} P(\bar{D}|\bar{R}) \sum_{\bar{E} \subseteq E_{\bar{D},\bar{R}}} P(\bar{E}|\bar{D}, \bar{R}) U_{\mathcal{C}^*_{\bar{S}}}. \end{aligned} \tag{3.5}$$

Multiple donors can be considered in settings where selection is restricted to cycles and chains only, in which case calculations are simplified. In such settings, we assume that, in cases where more than one donor from a pair match with a candidate, fallback options can be arranged using the alternate donors. Suppose for any $v_i \in V, v_j \in V^P, i \neq j$, that the donors $D_i = \{d_{i1}, d_{i2}, ..., d_{iM_i}\}$ are ordered such that $u_{i1j} \geq \cdots \geq u_{iM_ij}$. Without loss of generality, if there is no match between the donor $d_{im} \in D_i$ and r_j, we have that $u_{imj} = 0$.

In the case of cycles, we can correct the utility of a transplant between two pairs v_i and v_j to account for the multiple donors as follows. First let $u_{ij}^{\dagger}$ represent a "corrected" utility between v_i and v_j, reflecting the possibility of having to fall back to an alternate donor. We begin by taking the maximum utility match in E_{ij}, and multiply the utility by the probabilities of the corresponding donor being available and the match proving to be viable. Next, we add the utility of the second-best match, multiplied by the probabilities of that match proving to be viable and the donor involved being available, as well as the probability of the superior match failing, either due to non-viability of the match or unavailability of the donor. This is followed by the addition of the utility of the third-best match, multiplied by its probability of viability and the probability of availability of the corresponding donor, as well as the probability of the two superior matches failing. This procedure continues for all donors D_i. In other words, we have that

$$u_{ij}^{\dagger} = q_{i1}^{d} p_{i1j} u_{i1j} + \sum_{m=2}^{M_i} q_{im}^{d} p_{imj} u_{imj} \prod_{t=1}^{m-1} (1 - q_{it}^{d} p_{itj}). \tag{3.6}$$

Then, the "corrected" probability of a given donor in D_i being selected for transplantation is similarly given by the sum of the probabilities of success of each donor multiplied by the probability of success of the corresponding match, further

multiplied by the probability that superior matches fail, such that

$$p^{\dagger}_{ij} = q^{d}_{i1}p_{i1j} + \sum_{m=2}^{M_i} q^{d}_{im}p_{imj}\prod_{t=1}^{m-1}(1 - q^{d}_{it}p_{itj}). \tag{3.7}$$

For $c = \langle v_1, ..., v_\ell \rangle$, the expected utility is therefore given by:

$$EU_c = \left\{ q^{r}_{\ell}p^{\dagger}_{\ell 1}\prod_{k=1}^{l-1} q^{r}_{k}p^{\dagger}_{k\ k+1} \right\} \left\{ \frac{u^{\dagger}_{\ell 1}}{p^{\dagger}_{\ell 1}} + \sum_{k=1}^{l-1}\left(\frac{u^{\dagger}_{k\ k+1}}{p^{\dagger}_{k\ k+1}} \right) \right\}, \tag{3.8}$$

where the first term represents the probability that all candidates are available at the time of transplantation, and the second term represents the corrected utility of the cycle, accounting for fallbacks to alternate donors.

In the case of chains, we adapt the formulas from Dickerson et al. (2013) for pairs with more than one donor. The expected utility of a chain $c' = \langle v_0, v_1, ..., v_\ell \rangle$ is given by:

$$\begin{aligned} EU_{c'} = &\sum_{k=1}^{\ell-1}\left\{ \left(1 - q^{r}_{k+1}p^{\dagger}_{k\ k+1}\right)\left(\prod_{t=0}^{k-1} q^{r}_{t+1}p^{\dagger}_{t\ t+1}\right)\left(\sum_{t=0}^{k-1}\frac{u^{\dagger}_{t\ t+1}}{p^{\dagger}_{t\ t+1}}\right)\right\} \\ &+ \left(\prod_{k=0}^{\ell-1} q^{r}_{k+1}p^{\dagger}_{k\ k+1}\right)\left(\sum_{k=0}^{\ell-1}\frac{u^{\dagger}_{k\ k+1}}{p^{\dagger}_{k\ k+1}}\right). \end{aligned} \tag{3.9}$$

The first summand accounts for situations where the chain results in a transplant to r_k, $k \in \{1, ..., l-1\}$, but with failure occurring as part of the transplant to r_{k+1}. The second summand accounts for the complete chain being realized.

As in the single-donor case, we can enumerate each potential solution within a given LRS and use the inclusion-exclusion method to calculate the probabilities needed for expected utility calculation. Suppose we have K potential solutions, denoted $C^*_1, \ldots, C^*_K$, arranged in decreasing order of their total utilities $U_{C^*_1} \geq ... \geq U_{C^*_K}$. Note that potential solutions consisting of the same pairs, but with different donors facilitating the transplant, are distinct. Let $C^*_k = (V_{C^*_k}, E_{C^*_k})$ also represent the event that C^*_k is viable. Considering the probability associated with the specific

donor involved in each transplant, the probability that the potential solution is viable is given by

$$P(C_k^*) = \prod_{\{i,m,j\}:e_{imj}\in E_{C_k^*}} q_{im}^d q_j^r p_{imj}. \tag{3.10}$$

The higher-order joint probabilities are calculated analogously to (2.8). The probability P_k that the potential solution C_k^* is realized within this LRS is again given by (2.9) and the expected utility is calculated as (2.10). Similarly, the matrix formulation and Monte Carlo estimation described in Sections 2.3.3 and 2.3.4 can also be generalized in a straightforward fashion, by extending cells in the matrix to accommodate each possible donor, candidate, and match.

3.3 State Transition Model for Donor and Candidate Availability

We describe here a state transition model for donor and candidate availability, meant to replicate the patterns of activity observed among donors and candidates in real-life KPD programs. Suppose candidates and donors can be in one of three states. Participants that are designated as "Active" are available for transplant within the KPD. Donors or candidates designated as "Inactive" are not available for transplantation, say due to illness, but otherwise remain part of the program. Participants who are "Withdrawn" have been permanently removed from the program due to illness, death or other extenuating circumstances.

Designate the three states as 1 ="Active", 2 ="Inactive", and 3 ="Withdrawn". The transitions between these states can be specified by the following intensity matrix :

$$Q = \begin{pmatrix} -(\lambda_{A\to I} + \lambda_{A\to I}) & \lambda_{A\to I} & \lambda_{A\to W} \\ \lambda_{I\to A} & -(\lambda_{I\to A} + \lambda_{I\to W}) & \lambda_{I\to W} \\ 0 & 0 & 0 \end{pmatrix}. \tag{3.11}$$

where the ij-th entry of Q is such that $q_{ij} = \lim_{h \to 0^+} P\left(X(t+h) = j | X(t) = i\right)/h$ (note that $i \neq j$), where $X(t)$ represents the state occupied at time t. Withdrawal represents an absorbing state.

The time an individual donor or candidate spends in the active state follows an exponential distribution with rate $\lambda_{A\to I} + \lambda_{A\to W}$. At the end of this time interval, the individual either moves to the inactive state with probability $\lambda_{A\to I}/(\lambda_{A\to I} + \lambda_{A\to W})$ or is withdrawn from the pool with probability $\lambda_{A\to W}/(\lambda_{A\to I} + \lambda_{A\to W})$. Similarly, we assume the time spent in the inactive state follows an exponential distribution with rate $\lambda_{I\to A} + \lambda_{I\to W}$, after which the individual either becomes active again with probability $\lambda_{I\to A}/(\lambda_{I\to A} + \lambda_{I\to W})$, or is withdrawn from the pool with probability $\lambda_{I\to W}/(\lambda_{I\to A} + \lambda_{I\to W})$. This process continues until the individual is withdrawn.

Assuming the donor or candidate is active at the time of selection, and that transition to either inactive status or withdrawal signals that the donor or candidate in question is no longer considered for the transplant, then the probability of availability for transplantation, either q^d_{im} in the case of a donor or q^r_i in the case of a candidate, is given by $e^{-T(\lambda_{A\to I} + \lambda_{A\to W})}$, where T represents the interim time between selection and transplantation.

3.4 Simulation

We again perform 200 iterations of a dynamic KPD program under a variety of settings, in a similar setup to Ashlagi et al. (2011) and Bray et al. (2015). Here, we are primarily concerned with the number of realized transplants as well as waiting times for candidates in the simulated KPD programs. In this simulation, donor-candidate pairs and NDDs join our simulated KPD in continuous time by a Poisson process over 8 months, with a match run occurring at the end of each month. A

mean of 24 pairs and 1 NDD join each month.

Pairs are generated similarly to the previously reported simulations in Section 2.4. For each candidate r_i, either one or two associated donors are randomly generated, with $P(M_i = 2) = 1 - P(M_i = 1) = \rho$. Donors are generated until the specified number of incompatible donors are obtained, with those generated that are found to be compatible with the candidate discarded. We consider settings with $\rho \in \{0, 0.2, 0.4\}$.

When a new pair or NDD joins the pool, each of the added donors is assessed for compatibility by virtual crossmatch with all candidates currently in the pool, and all donors currently in the program are assessed for compatibility with the new candidate. Each individual donor and candidate joins the pool in the active state. Match failure rates are set according to the panel reactive antibody (PRA) value of the candidate as in Section 2.5. A utility value of 1 is assigned to each match, such that the outcome of interest is effectively in terms of the number of realized transplants.

Availability of individual donors and candidates for transplantation are assumed to follow independent state transition models as described in Section 3.3. Appropriate values for $\lambda_{A\to I}$, $\lambda_{A\to W}$, $\lambda_{I\to A}$, and $\lambda_{I\to W}$ are determined based on the following assumptions. We assume the individuals spend 80% of the time in the active state and 20% of the time in the inactive state, with average times of about 4 months and 1 month in the active and inactive states respectively, and that the overall withdrawal rate is approximately 2%. Further, we assume that withdrawals are three times as likely while inactive than while active. To summarize, we have that $\lambda_{A\to I} + \lambda_{A\to W} = 0.25$, $\lambda_{I\to A} + \lambda_{I\to W} = 1$, $\lambda_{A\to W} + \lambda_{I\to W} = 0.02$, $\lambda_{I\to W} = 3\lambda_{A\to W}$. Solving, we obtain $\lambda_{A\to I} = 0.245$, $\lambda_{A\to W} = 0.005$, $\lambda_{I\to A} = 0.985$,

and $\lambda_{I \to W} = 0.015$. A pair is available for a match run if both the candidate and at least one donor is available, otherwise, it is not included in the match run. NDDs are assumed to be available throughout the simulation.

We compare results for selection based on LRSs to those based on simple cycles and chains (the Cycles and Chains setting). We also compare results between candidates who join with two donors as opposed to one. At each match run, the optimal solution, consisting of either cycles and chains or LRSs, depending on the current setting, is collected. LRSs are constrained to a maximum of size 4, with sub-cycles constrained to size 3, and sub-chains to length 3. Each cycle, chain, or LRS is then assigned a utility value. In the Cycles and Chains setting, the simple utility consisting of the sum of the utilities of the consituent matches is assigned, though we allow fallbacks to the second donor where possible, as well as sub-chains of the original chain. In the LRS setting, exact expected utilities are assigned, accounting for uncertainty and fallback options, with the best remaining option after evaluation within each LRS ultimately transplanted.

Transplantation is assumed to take place immediately prior to the next match run, with the interim time (1 month) representing the time needed to assess compatibility and availability. Each donor, candidate and match within the selected transplant arrangements are evaluated and failures are determined. Candidates and donors who were selected but become unavailable in the interim are marked as unable to participate in the transplant arrangement for the remainder of this evaluation. For all matches that remain, success probabilities are updated after evaluation, to 1 if successful and 0 otherwise, for use in future calculations. Pairs and NDDs that were included in transplant arrangements but not involved in an exchange are returned to the KPD to participate in the next match run. For transplanted chains, the final

donor is retained as a bridge donor, acting as a NDD in future match runs. For more details about the simulation, we refer the reader to Bray et al. (2018).

Table 3.1: Average number of realized transplants and proportion of transplanted candidates across 200 simulations of a dynamic KPD program.

		Cycles and Chains		Locally Relevant Subgraphs	
Prob. of 2nd Donor	Candidates	Realized Transplants	Proportion Transplanted	Realized Transplants	Proportion Transplanted
0	All Candidates	30.61	0.158	43.92	0.226
0.2	Candidates with 1 Donor	25.91	0.168	35.65	0.230
	Candidates with 2 Donors	10.36	0.260	15.92	0.399
	All Candidates	36.27	0.187	51.56	0.265
0.4	Candidates with 1 Donor	20.96	0.180	27.21	0.233
	Candidates with 2 Donors	20.72	0.266	31.86	0.409
	All Candidates	41.68	0.214	59.07	0.303

Results are displayed in Table 3.1. As expected, we observe improvement, in terms of proportion of candidates transplanted, in the LRS approach over the classical strategy based on simple cycles and chains. Two-donor candidates are shown to be more likely to receive transplants in all settings as well. Kaplan-Meier curves showing the candidate waiting time until transplantation under each simulation setting are shown in Figure 3.2, with $\rho = 0$ on the leftmost chart, $\rho = 0.2$ in the center, $\rho = 0.4$ on the right. We observe a greater proportion of candidates with two donors receiving transplants across the timeline of the simulation compared to candidates with a single donor, in both the Cycles and Chains and Locally Relevant Subgraphs settings.

3.5 Discussion

In this chapter, we proposed further generalizations to the KPD model, to account for candidates joining a program with several incompatible donors, and

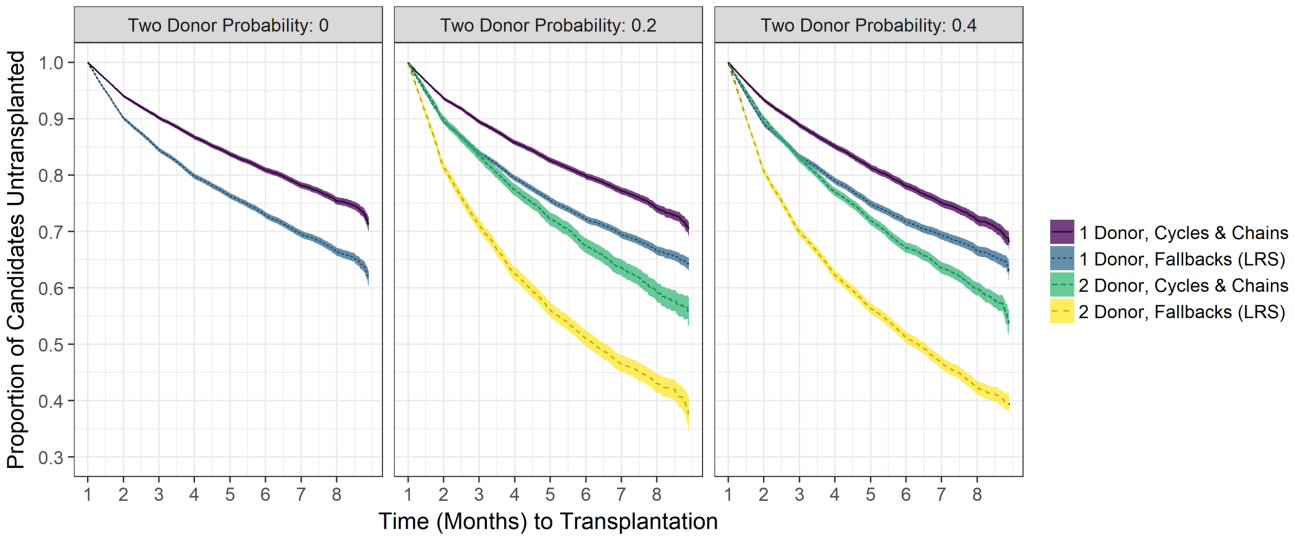


Figure 3.2: Kaplan-Meier curves for wait times of candidates across 200 simulations.

with a state transition model for individual donor or candidate failure. Additional donors benefit both their candidate and the KPD program as a whole by introducing new transplant opportunities, as well as additional fallback options for their paired candidate, thereby increasing the number of transplant arrangements and potential solutions in which the candidate is involved.

Here, we assume independence between the sources of potential failures, namely the donors, candidates, and matches. There are clearly factors that may affect the probability of availability after identification of a suitable exchange, for reasons such as unanticipated scheduling issues or candidates becoming too ill to proceed to transplantation, among others, but there do not exist sufficient data to estimate these probabilities accurately. Fumo et al. (2015) report on investigations into failed transplant offers, though these relate largely to match failures and candidate refusals, as opposed to donor or candidate-specific failures. Future studies to explore probability assignments in greater detail, preferably through a statistical model of probabilities developed using clinical data, may be warranted, though

data supporting more complicated models may not be easily available.

Related studies include investigations by Farina et al. (2017), who propose their generalized approach to kidney exchange, which allows more than one donor to participate in KPD with a given patient, and also allows for the possibility of a donor willing to donate if any of a number of patients receive kidneys. Nicolo and Rodríguez-Álvarez (2012) propose a framework inspired by the concept of exchange among organ clubs. These clubs extend the notion of donor-candidate pairs, allowing for a set of healthy donors equally willing to donate one of their kidneys in exchange for an equal or greater number of kidneys received by a target set of patients. While these situations may not be common in practice, our proposed models may be further generalized to account for uncertainty and fallback options in the setting of kidney exchange clubs.

CHAPTER IV

On Modeling Temporal Aspects of Kidney Paired Donation

4.1 Introduction

KPD is an inherently temporal problem, with the composition of the pool constantly changing as pairs and NDDs join and depart the KPD program for various reasons, including transplantation and withdrawal, and potential matches determined by virtual crossmatch are confirmed or rejected over time. These temporal aspects, combined with the fact that algorithmic solutions in KPD are myopic in nature, lead to certain inefficiencies, indicating the need for adaptive strategies for organ allocation.

One salient feature of KPD programs is that patients can generally be characterized by their difficulty to match with donors in the pool, with most of the difficult-to-match candidates being highly sensitized against foreign HLA (Ashlagi et al., 2013). The level of sensitization of a transplant candidate is typically summarized by the PRA, where a PRA value of x suggests that the candidate is expected to be unable to match with $x\%$ of the population. In the United States, there are an estimated 14,000 kidney transplant candidates with a PRA greater than 80 on the deceased donor waitlist (Velidedeoglu et al., 2018). In current practice, KPD programs mostly benefit pairs that are easy-to-match, who form

exchanges rapidly among themselves (Segev et al., 2008). The few options for difficult-to-match pairs that may have existed are lost as their potential exchange partners are quickly matched, transplanted, and depart from the program.

Figure 4.1 illustrates an example of a small KPD pool, initially comprising three pairs at time t_1, including a pair with a difficult-to-match patient A, and two other pairs, B and C. An additional pair D joins the pool at a later time t_2. In Figure 4.1(a), at time t_1, pairs B and C can form a 2-way exchange, though a match exists between B and difficult-to-match patient A. If this exchange proceeds to transplantation before pair D joins the pool at t_2, as in Figure 4.1(b), we lose the match to A from B, and while the donor of A is found to match with the candidate of D, we must wait again for a new pair to match with A so that it may form part of an exchange cycle. Alternatively, by postponing transplantation until after t_2 as in Figure 4.1(c), new pair D is found to form a 3-way exchange with B and difficult-to-match pair A. With three realized transplants, this solution is clearly the most desirable option in the $[t_1, t_2]$ time period, especially considering the opportunity for A to participate in a cycle. The ability to transplant the larger cycle, including the difficult-to-match patient with a rare compatible donor, would be lost by performing the immediately available 2-way exchange between the two easy-to-match pairs at t_1. According to Sönmez and Ünver (2017), optimizing KPD in a greedy fashion leaves the possibility that fewer overall transplants will ultimately be conducted.

Dickerson et al. (2014) posit that the prioritization of transplant opportunities for the most difficult-to-match patients is currently one of the most contentious issues in KPD. The standard model of KPD optimization tends to leave the pool in a depleted state, with the remaining patients being largely difficult-to-match (Awasthi and Sandholm, 2009). KPD optimization algorithms should be designed

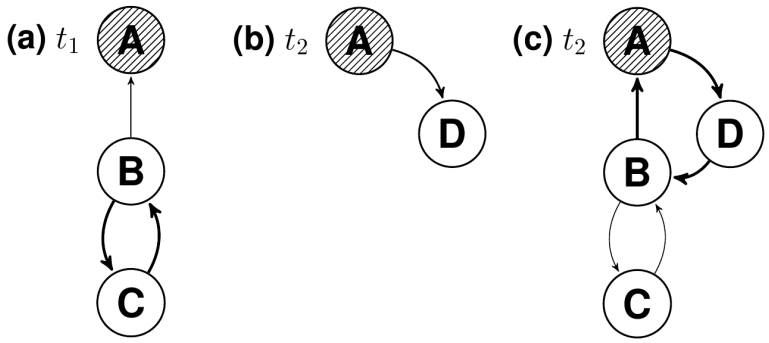


Figure 4.1: Example of (a) a small KPD pool with a pair that includes a difficult-to-match patient, A, and two regular pairs, B and C, at time t_1, (b) the pool after pair D joins at time t_2 if the 2-way exchange between B and C is transplanted, and (c) the pool after pair D joins at time t_2 if B and C remain in the pool.

to maximize the long-term utility, incorporating considerations that allow preservation of compatible matches involving difficult-to-match pairs for future exchanges.

Here, we attempt to capture the dynamics within a typical KPD program as a first step toward an adaptive allocation policy for pairs. We propose to model the progression of the KPD network via a 3-dimensional tensor, containing the sequence of matrices that represent the compatibility of pairs in the pool. By employing decomposition techniques on this tensor, we can extract low-dimensional features, characterizing the pairs based on their propensity to match and form exchanges over time. These characterizations can then be used to inform an allocation policy that, say, preserves matches for difficult-to-match patients over a reasonable time horizon. We also briefly outline alternative techniques for modeling the temporal progression of a KPD program.

Note that, in this setting, we only consider single donor-candidate pairs. In other words, we do not consider NDDs, and candidates join with only one incompatible donor.

4.2 Tensor Preliminaries

We begin with an introduction to the basic tensor framework pertaining to our proposed temporal model. We then describe the application of tensors in the KPD context in Section 4.3. For additional background, Kolda and Bader (2009) provides a comprehensive review of tensor analysis and decomposition.

4.2.1 Basics of Tensor Analysis

An N-dimensional or N-th order tensor is an element of the tensor product of N vector spaces. In other words, an N-dimensional tensor can be denoted as $\mathcal{Y} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$, where $N \in \{1, 2, \dots\} = \mathbb{N}^+$, and for $n = 1, 2, \dots, N$, $I_n \in \mathbb{N}^+$. A tensor is essentially a higher-order analogue to vectors and matrices, where the former can be regarded as first-order tensors, and the latter as second-order tensors. Certain vector and matrix concepts can be extended to higher-order tensors. For example, the norm of a tensor $\mathcal{Y}$ is the square root of the sum of the squares of all of its elements, or $\|\mathcal{Y}\| = \sqrt{\sum_{i_1=1}^{I_1} \sum_{i_2=1}^{I_2} \cdots \sum_{i_N=1}^{I_N} x_{i_1 i_2 \cdots i_N}^2}$.

Fibers, the higher-order analogue to matrix rows and columns, are defined as column vectors of a tensor, obtained by fixing every index of the tensor but one. Similarly, two-dimensional sections of a tensor are referred to as slices, defined by fixing all but two indices of the tensor. The mode-n matricization of tensor $\mathcal{Y}$, denoted $Y_{(n)}$, arranges the mode-n fibers into columns, resulting in a flattening of the tensor into a matrix. Note that the specific permutation of columns in a matricization is not important, so long as it is consistent across related calculations. Certain matrix multiplications are important in the context of tensors. In particular, the Khatri-Rao product of matrices $A \in \mathbb{R}^{I \times K}$ and $B \in \mathbb{R}^{J \times K}$, denoted by $A \odot B \in \mathbb{R}^{(IJ) \times K}$, is

defined as

$$A \odot B = \begin{bmatrix} a_1 \otimes b_1 & a_2 \otimes b_2 & \cdots & a_K \otimes b_K \end{bmatrix}, \tag{4.1}$$

where $\otimes$ represents the Kronecker product.

We can construct a third-order tensor $\mathcal{Y}$ as a sequence of matrices, each matrix forming a slice of the tensor. For temporal network data, these matrices are typically the adjacency matrices W^t of a network from times $t = 1, \ldots, T$, where $w_{ij}^t = 1$ if an edge exists between vertices i and j, and $w_{ij}^t = 0$ otherwise. Figure 4.2 illustrates the form of such a $\mathcal{Y}$ across 4 time points.

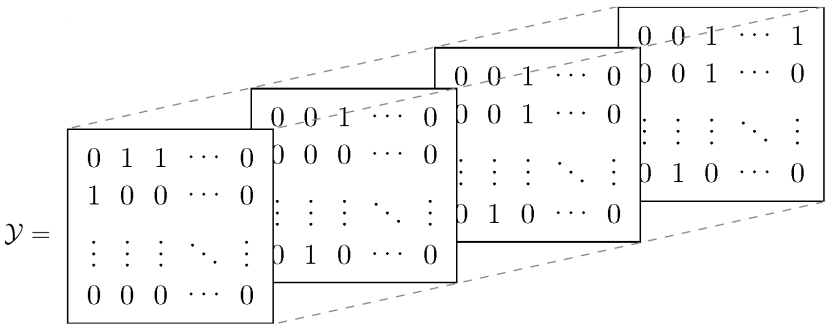


Figure 4.2: Illustration of a sequence of network adjacency matrices across four timepoints as a 3-dimensional tensor.

4.2.2 Tensor Decomposition

We can decompose complex multi-dimensional patterns and extract lower-dimensional features from a tensor by leveraging higher-order structure and correlations within the data. Traditional matrix decomposition techniques are inadequate when dealing with multidimensional or temporal data, as flattening data into matrices can obscure important relations among variables. Tensor decomposition has proven useful in domains such as data mining, dimensionality reduction, pattern recognition and classification (Cichocki and Phan, 2009).

We first describe for context a basic method of tensor decomposition, the CP decomposition, before turning attention to extensions appropriate for the KPD

setting. An N-th order tensor $\mathcal{Y}$ is considered rank-one if it can be written as the outer product of N vectors, such that $\mathcal{Y} = a^{(1)} \circ a^{(2)} \circ \cdots \circ a^{(N)}$, where $y_{i_1 i_2 \cdots i_N} = a^{(1)}_{i_1} a^{(2)}_{i_2} \cdots a^{(N)}_{i_N}$, $\forall 1 \leq i_n \leq I_n$. The CP decomposition, short for "Canonical Decomposition/Parallel Factors", factorizes a tensor into a sum of component rank-one tensors (Cichocki and Phan, 2009). These components can be interpreted as latent features of the data.

An approximation to 3-dimensional $\mathcal{Y} \in \mathbb{R}^{I \times J \times K}$ can be obtained as the sum of $R \in \mathbb{N}^+$ rank-one tensors. In other words, the decomposition takes the form $\mathcal{Y} \approx \sum_{r=1}^{R} a_r \circ b_r \circ c_r$, where $a_r \in \mathbb{R}^I$, $b_r \in \mathbb{R}^J$, and $c_r \in \mathbb{R}^K$ for $r = 1, ..., R$, with R being the number of components in the tensor approximation. Concisely, we can denote the CP decomposition as $\mathcal{Y} \approx [\![\lambda; A, B, C]\!] \equiv \sum_{r=1}^{R} \lambda_r a_r \circ b_r \circ c_r$, where the factor matrices $A \in \mathbb{R}^{I \times R}, B \in \mathbb{R}^{J \times R}$, and $C \in \mathbb{R}^{K \times R}$ denote the concatenation of vectors from the rank-one components into matrices, such that $A = [a_1 \; a_2 \; \cdots \; a_R]$, and similarly for B and C. Columns of A, B, and C are normalized to length one, with the weights absorbed into the vector of coefficients $\lambda = [\lambda_1 \ldots \lambda_R]^T \in \mathbb{R}^R$.

Factors A and B encode the community structure of the network (Gauvin et al., 2014). Elements a_{ir} and b_{ir} describe the weight of the outgoing and incoming membership of vertex i to component r, respectively. Factor C gives the temporal activity of each community, where elements c_{kr} associate component r to the time intervals k it spans, indicating activity level of each component as a function of time. We note that the choice of R amounts to finding number of components that best explain the tensor structure. With R too low, we obtain only the strongest components, potentially overlooking important features. Conversely, an R too high risks overfitting the data.

The relation between $\mathcal{Y}$ and its constituent factors are given by $X_{(1)} \approx A(C \odot$

$B)^T$, $X_{(2)} \approx B(C \odot A)^T$, and $X_{(3)} \approx C(B \odot A)^T$, relating the matricizations along each of the tensor modes to Khatri-Rao products among the factors (Kolda and Bader, 2009). Based on this relation, an alternating least squares (ALS) approach can be employed to find factor matrices for a given tensor algorithmically. An ALS procedure for obtaining the factors starts by fixing B and C to solve for A, followed by fixing A and C to solve for B and finally fixing A and B to solve for C, continuing in this manner until some convergence criterion is satisfied. If we suppose B and C are fixed, solving for A is equivalent to solving the minimization problem of the form:

$$\min_{\hat{A}} \left\| X_{(1)} - \hat{A}(C \odot B)^T \right\|_F, \tag{4.2}$$

where $\|\cdot\|_F$ denotes the Frobenius norm, such that for arbitrary matrix M, $\|M\|_F = \sqrt{tr(MM^T)}$. The update rule for A is given by $A \leftarrow X_{(1)} \left[(C \odot B)^T\right]^\dagger$. Updates to B and C are obtained in an analogous fashion. While we focus on 3-dimensional tensors here, this procedure can be generalized for N-th order tensors.

4.3 Adapting Kidney Paired Donation for Tensor Decomposition

We model the sequence of adjacency matrices over time in a KPD program as a 3-dimensional tensor. This tensor describes the time-course progression of compatibility of pairs in a KPD pool, encoding both the topological and temporal information of the donor-candidate pairs. In this case, the first and second modes, given by the rows and columns of the tensor respectively, represent donor and candidate connectivity, while the third mode represents progression of compatibility over time. We seek the CP decomposition $\mathcal{Y} \approx [\![\lambda; A, B, C]\!]$. In the KPD setting, factors A and B can be interpreted as the "donor" and "candidate" factors, where elements describe the weight of the outgoing and incoming matches

of pair i to component r respectively.

Given the KPD network is constantly evolving, it would be preferable to adaptively update pre-existing results given new data, without having to re-compute the decomposition whenever new data arrives. Zhou et al. (2016) detail an Accelerating Online Tensor Decomposition for third-order tensors to update decomposition results in an online manner as new tensor slices are observed. The temporal factor $C = [C^{(1)}\ C^{(2)}]^T$ is updated by fixing A and B, and solving

$$C \leftarrow \underset{C}{\operatorname{argmin}} \left\| \begin{bmatrix} Y_{old(3)} - C^{(1)}(B \odot A)^T \\ Y_{new(3)} - C^{(2)}(B \odot A)^T \end{bmatrix} \right\|_F = \begin{bmatrix} C_{old} \\ C_{new} = Y_{new(3)}\{(B \odot A)^T\}^\dagger \end{bmatrix}, \tag{4.3}$$

where Y_{old} represents the entire matricized history of network observations thus far and Y_{new} represents a new matricized batch of network observations. The non-temporal factors are then updated, beginning with A. In Zhou et al. (2016), the update can be written in terms of Y_{new} and C_{new} via $A = PQ^{-1}$, where

$$P \leftarrow P + Y_{new(1)}(C_{new} \odot B)\ ;\ Q \leftarrow Q + (C_{new}^T C_{new}) * (B^T B), \tag{4.4}$$

with $*$ denoting element-wise matrix multiplication, and P and Q having been initialized at the beginning of the algorithm. Similarly, $B = UV^{-1}$, where U and V are analogous to P and Q, and with $Y_{new(2)}$ and A replacing $Y_{new(1)}$ and B in (4.4). To avoid negative elements in the tensor decomposition, we also consider penalizing such values by setting them to a small value ϵ, in a manner similar to the fast hierarchical ALS for non-negative tensor factorization (Cichocki and Phan, 2009).

As a proof of concept, we aim to assess the effectiveness of tensor decomposition in clustering pairs of different classes, say, easy versus difficult-to-match, in a small dynamic KPD program. We simulate such a program, generating easy-to-match and difficult-to-match single donor-candidate pairs entering the program over time. Ten

pairs at a time are added to the pool over 20 time periods, resulting in a total of 200 pairs. Pairs are generated with 50% probability of being designated easy-to-match, versus difficult-to-match. Matches between these pairs are generated such that 25%, 15% and 5% of possible connections are designated as potential matches between two easy-to-match pairs, an easy-to-match and a difficult-to-match pair, and two difficult-to-match pairs respectively. At regular intervals, a maximum utility cycle solution is selected and evaluated for transplantation. We assign probabilities of 10% and 25% of a match being overturned for an easy-to-match and difficult-to-match candidate respectively, leaving the cycle untransplanted. Finally, between match runs, we assign a probability of 10% of an untransplanted pair withdrawing from the pool.

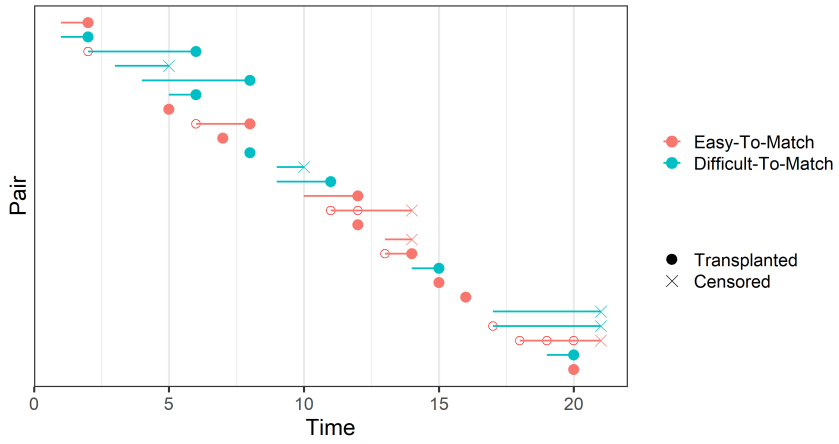


Figure 4.3: Trajectory of a subset of pairs in a simulated dynamic KPD program.

Figure 4.3 displays the trajectories of a subset of pairs in the simulation. Note that we observe 98/112 (87.5%) easy-to-match and 49/88 (55.7%) difficult-to-match pairs receiving transplants in this simulation, which is admittedly high compared to clinical practice. Figure 4.4 displays components of tensor decompositions in both "donor" and "candidate" factors recovered at the end of simulation. We observe

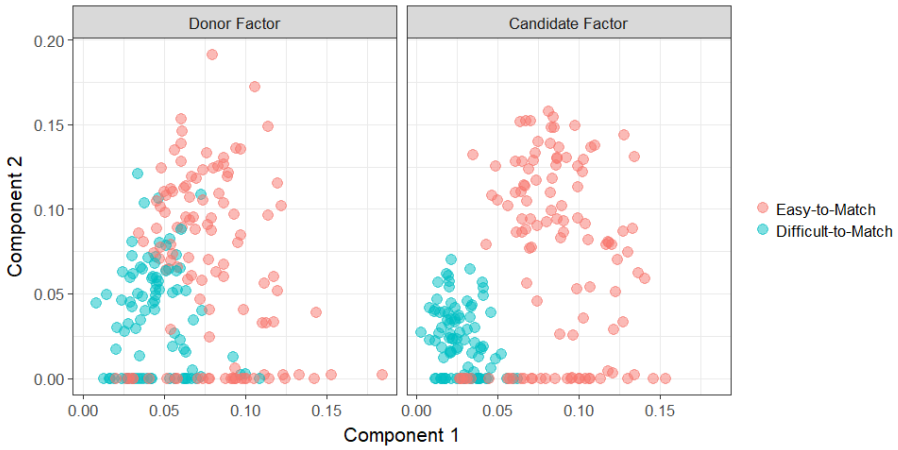


Figure 4.4: Tensor decomposition weights in components for both the "donor" and "candidate" factors in a simulated dynamic KPD program.

adequate separation between the easy-to-match and difficult-to-match clusters across factors, especially in the "candidate" factor. While the factors themselves may not have satisfying interpretation, the data patterns appear to be reasonably clear.

We note that standard CP decomposition, as well as the Accelerating Online Tensor Decomposition method by Zhou et al. (2016), are typically applied to continuous-valued tensors, whereas tensors that model connectivity over time, such as our history of KPD adjacency matrices, contain binary-valued elements. In principle, one can apply CP decomposition to a binary tensor, though such an approach may result in sub-optimal performance. In particular, predicted values can fall outside of the $[0, 1]$ range.

To address this issue, Wang and Li (2018) propose a tensor decomposition that can be viewed as a generalization of the classical CP decomposition to binary tensors, in a way that is analogous to how GLMs generalize the standard linear model. It is assumed that entries in binary tensor $\mathcal{Y}$ are realizations of independent Bernouilli random variables, in that $\mathcal{Y}|\Theta \sim Ber\left(f\left(\Theta\right)\right)$, with $P(y_{i_1 i_2 \cdots i_N} = 1) = f(\theta_{i_1 i_2 \cdots i_N})$. Here, the parameter tensor $\Theta = [\theta_{i_1 i_2 \cdots i_N}]$ is the unknown object of interest. In the

KPD context, this could represent the underlying time-course propensities for pairs to match, for example. Entries of $\mathcal{Y}$ are assumed to be mutually independent conditional on Θ, where Θ admits a rank-R CP decomposition, such that $\Theta = \sum_{r=1}^{R} \lambda_r a_r^{(1)} \circ \cdots \circ a_r^{(N)}$. The function f is a known link function, analogous to link functions for GLMs with binary outcomes, such as the logit link function. The authors propose a rank-constrained likelihood-based estimation for Θ under the constraints that Θ admits a rank-R CP decomposition, and that all the entries of Θ are bounded in absolute value by a constant $\alpha \in \mathbb{R}^+$. While these constraints render the problem non-convex, by using a similar principle as in ALS, the optimization becomes convex for each block of parameters while holding the others fixed.

One drawback of the techniques described above in the KPD setting is that dimensions are assumed to stay fixed, or only grow temporally in the case of Zhou et al. (2016), such that the addition and departure of vertices over time are not handled adaptively. In this case, one needs to pre-allocate space in a large tensor in order to model the augmenting network. Fibers of the tensor involving such a pair will have entries of 0 until such time that the pair joins the network, which may lead to issues in interpretation.

4.4 Alternative Methods to Model Temporal Kidney Paired Donation

We discuss here alternative methods to model temporal aspects of a KPD program, outside of the tensor framework.

Xu (2015) proposes the stochastic block transition model (SBTM), which allows the presence of a future edge in an evolving network to depend both on the current network states and whether or not an edge is currently present, with vertices and edges joining and departing the network as time progresses. Vertices can belong to

one of a set of K classes, with c denoting the class membership vector such that $c_i = k$ denotes that vertex i belongs to class k, where $k \in \{1, \ldots, K\}$. Note that vertices can change class over time. The main idea behind the SBTM is as follows. Let W^t and c^t represent an adjacency matrix and class membership vector at time t, with $W^{(T)}$ and $c^{(T)}$ denoting the sequence of adjacency matrices and class membership vectors over a timespan of $\{1, \ldots, T\}$. For any pair of vertices i and j, in classes a and b respectively, that exist at both times $t-1$ and t and with an edge between them at time $t-1$ (i.e. $w_{ij}^{t-1} = 1$), the w_{ij}^t are independent and identically distributed. The same is true if $w_{ij}^{t-1} = 0$. Thus, all edges, as well as non-edges, in a block at time $t-1$ are equally likely to re-appear at time t. Edges are formed according to two block transition matrices: $\Pi^{t|0} = [\pi_{ab}^{t|0}]$, where $\pi_{ab}^{t|0} = P(w_{ij}^t = 1 | w_{ij}^{t-1} = 0)$, denotes the probability of a new edge forming within each block, and $\Pi^{t|1} = [\pi_{ab}^{t|1}]$, where $\pi_{ab}^{t|1} = P(w_{ij}^t = 1 | w_{ij}^{t-1} = 1)$ denotes the probability of existing edges re-occurring within each block.

In this context, modeling the KPD as a SBTM would serve a similar means as the tensor decomposition. The class memberships are analogous to the clusters from the tensor decompositions in the previous section. These memberships are assigned based on an approximate inference procedure using a combination of an extended Kalman filter and a local search algorithm (Xu, 2015). Note that the ability to form new matches among already observed pairs in a KPD would typically not be possible. However, new compatibilities could arise, say, if one were to consider the possibility of candidates seeking additional donors to join KPD with them over time, or other situations such as desensitization (see Section 6.1.2).

KPD can also be described in the context of sequential decision-making. At any given time, we have that the KPD program is in some state (e.g. a network

of pairs and matches), at which point an action can be taken (e.g. proceed with an exchange cycle), with a reward (e.g. successful transplants, realized utility) or penalty (e.g. failed matches) observed. Approaches that model KPD via sequential decision-making attempt to make the problem less myopic and more anticipatory.

Sequential decision making in KPD has commonly been applied to the problem of NDD allocation. Li et al. (2014a) propose an approach to sequentially allocate NDDs so as to maximize the expected utility over a given number of actions. Given that a long pre-specified chain cannot commonly be implemented to completion in practice, their model sees chains extended sequentially in a near-optimal manner by selecting one potential transplant recipient at a time. Wang et al. (2017) extends the idea by selecting chains of a set length using a look-ahead strategy, where the value of each potential chain is assessed by taking account of the value of the bridge donor to the future KPD pool.

Awasthi and Sandholm (2009) employ an online stochastic optimization algorithm to kidney exchange, where subsets of the possible future trajectories of the KPD are sampled and solved. Based on these trajectories, scores are assigned to each possible exchange at the current time, and the set of such exchanges that produces the most favorable score is selected. This approach is unique in the KPD literature in that it attempts to anticipate the formation of future exchanges and adjusts allocation policy based on these future trajectories.

4.5 Discussion

In this chapter, we address temporal aspects in KPD management. In particular, we propose to employ tensor decomposition to uncover latent features in a 3-dimensional representation of the progression of a KPD pool over time,

characterizing the propensity of pairs to form matches. Other techniques to model dynamic KPD programs are also outlined. Issues with tensor decomposition procedures typically include selection of an appropriate number of components, and avoiding sub-optimal decompositions in local minima. These can be addressed by cross-validation and multiple initialization respectively. Future considerations include adapting decomposition techniques for tensors that grow and shrink along the compatibility modes, as pairs join and depart the underlying network.

Ultimately, clustering patterns or class assignments obtained as a result of these techniques would be used to improve transplant allocation policy so as to account for the transplantation windows for difficult-to-match pairs and preservation of matches among them. The ethics involved in withholding pairs for transplantation represent an important consideration for such procedures to be implemented. Ideally, consent would be required, and reasonable thresholds on waiting time would need to be enforced.

CHAPTER V

KPDGUI - Software for Management of Kidney Paired Donation Programs

5.1 Introduction

We describe here our software application, KPDGUI (Kidney Paired Donation Graphical User Interface), for optimization and management of a virtual KPD program. KPDGUI provides users an interactive environment through which a pool of incompatible donor-candidate pairs and NDDs can be visualized and customized, with preferred exchanges identified through optimization. While there exist software platforms for managing KPD programs, KPDGUI offers an interactive visual display of the current state of the KPD program, and implementation of optimization methods outlined in this dissertation.

5.2 Software Description

KPDGUI is written in C++, with the graphical user interface rendered using the Qt framework (The Qt Company). Solutions to the IP problem (2.1) are obtained using the linear programming software Gurobi 6.5.0 (Gurobi Optimization Inc.). The application, code, example files and video tutorials can be accessed at `https://github.com/mathieubray/KPDGUI`.

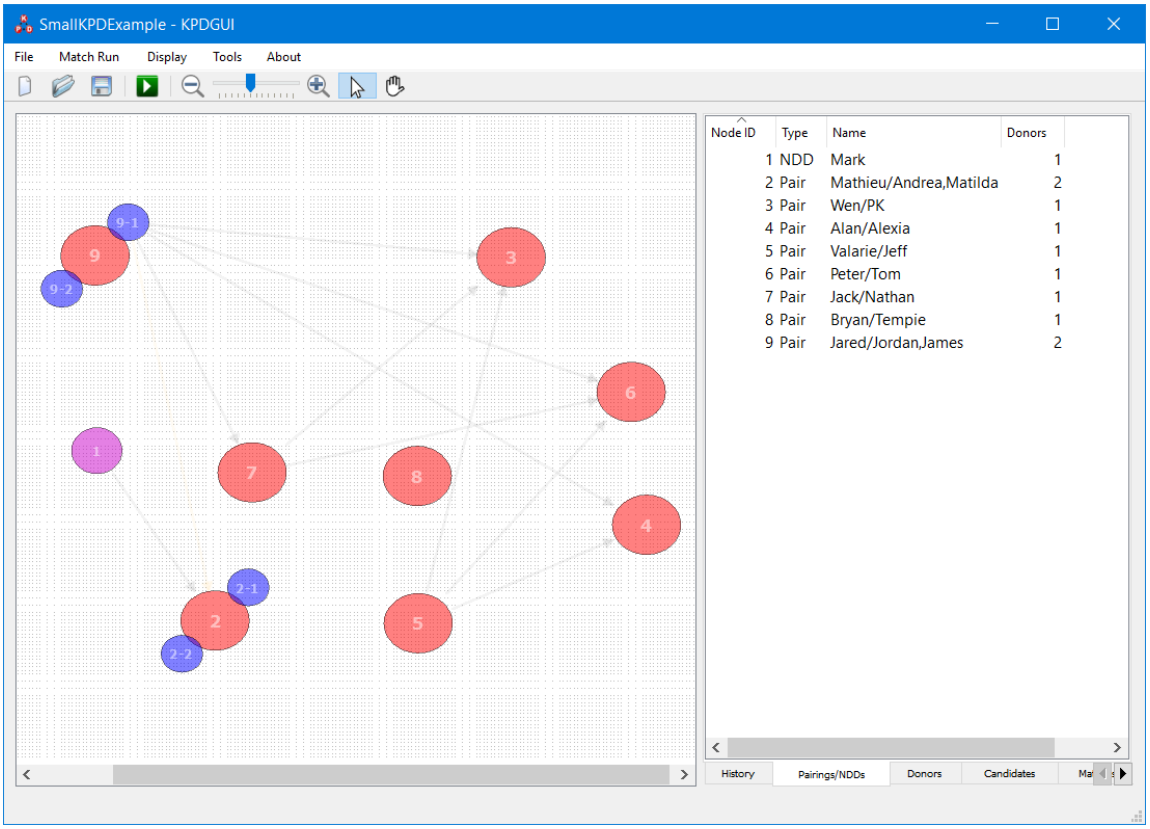


Figure 5.1: Main KPDGUI screen displaying a KPD pool consisting of 8 pairs (including 2 candidates with two paired donors each), 1 NDD, and the matches among them

5.2.1 The Virtual Kidney Paired Donation Program

Launching the application displays the main screen, which is divided into two panels (see Figure 5.1). On the left, the application visualizes the underlying network representation of the KPD. On the right are a number of tabs which contain information about the KPD, providing a running history of the commands used during the current session and storing attributes of pairs and NDDs, individual donors and candidates, matches, and cycles, chains, LRSs, and solutions identified in previous match runs.

The user can add pairs or NDDs and their characteristics individually to populate the KPD pool. Such characteristics include blood types and HLA information for donors and candidates, along with other clinical characteristics, such as age, sex,

Hepatitis C status for candidates, and cigarette smoking status for donors, among others. The user can also specify failure probabilities for the donors and candidates for calculations in optimization schemes involving fallback options. Alternatively, one can load an entire set of pairs and NDDs from a structured file that contains the required information for each pair and NDD. Note that more than one donor can be associated with each candidate.

Once added, pairs and NDDs are displayed as elliptical nodes in the network. Nodes representing pairs are displayed in red, while NDDs are displayed in purple. If the candidate joins with more than one donor, each donor is represented by a smaller blue node, grouped together with the candidate. Right-clicking an individual donor or candidate in the visual panel gives the option to edit the characteristics of the corresponding entity. In particular, the donor or candidate can be designated as excluded from future match runs.

Matches are automatically generated for new pairs and NDDs based on virtual crossmatches against all other pairs and NDDs already in the pool, comparing blood types and HLA information. Matches are represented by arrows, which originate from the donor and point to the matching candidate. If the virtual crossmatch between a donor and candidate fails, no arrow is added. The user can assign a custom transplant score to each match in the system, as well as change the failure probability for calculation in optimization schemes involving fallback options. The match can also be designated as excluded from future match runs.

5.2.2 Optimization

At any time, the user can trigger a match run, assessing the pool to find the optimal selection of cycles and chains or LRSs. Prior to the match run, the user specifies a number of parameters, in particular the optimization setting to employ,

among those studied in Chapters II and III. We re-iterate these settings here:

1. Cycles and Chains: The optimal solution is the set of disjoint cycles and chains that maximizes the total utility.
2. Cycles and Chains with Fallbacks: The optimal solution is the set of disjoint cycles and chains that maximizes the total expected utility, accounting for uncertainty and fallback options.
3. Locally Relevant Subgraphs: The optimal solution is the set of disjoint LRSs that maximizes the total expected utility, accounting for uncertainty and fallback options.

For each match run, the user provides upper bounds to the sizes of cycles and chains to be considered. An upper bound to the size of the LRSs must also be specified for the Locally Relevant Subgraphs setting, in which case the caps for cycles and chains refer to the sub-cycles and sub-chains considered within each LRS.

The user also specifies the utility to assign to each individual match. The default is a value of 1 for each match, representing the single potential transplant that can result. Alternatively, the user-specified transplant score can be employed as the utility. The estimated 5- or 10- year survival probability of the transplant, based on output from the graft survival calculator by Ashby et al. (2017) using clinical characteristics of the donor, candidate, and combination thereof provided by the user, can also be employed as the utility (see section 6.1.1 for further commentary on graft survival estimation).

Other parameters include the number of unique solutions to provide (in the sense that while certain exchanges may appear in more than one solution, the combination of selected exchanges will be different in each produced solution), and whether to

estimate or calculate the expected utility exactly. If estimating, the user also specifies the number of iterations to apply in the estimation procedure.

After a match run, each individual solution is added to the "Solutions" tab, and the set of all cycles, chains, and LRSs within these solutions is added to the "Possible Exchanges" tab. Selecting any of these will highlight the relevant matches in the visual representation of the network, and double-clicking will bring up information about the optimization settings used to generate the cycle, chain, LRS, or solution. The user can also cluster and isolate any selected cycle, chain, LRS, or solution.

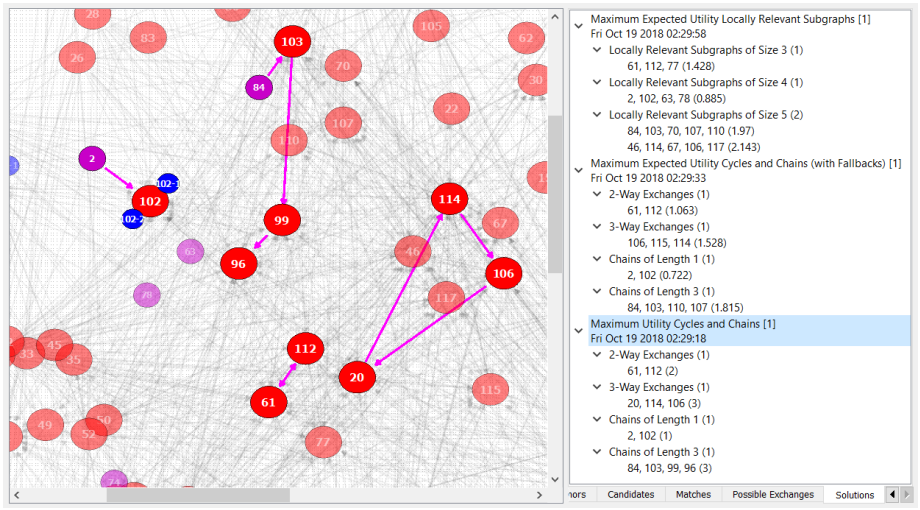
5.3 Example

We illustrate a typical use case of KPDGUI, applied to a synthetic KPD program, obtained by sampling de-identified historical data from the Alliance for Paired Donation. The virtual program consists of 107 donor-candidate pairs, including 5 candidates with two incompatible donors and 1 candidate with three such donors, and 11 NDDs.

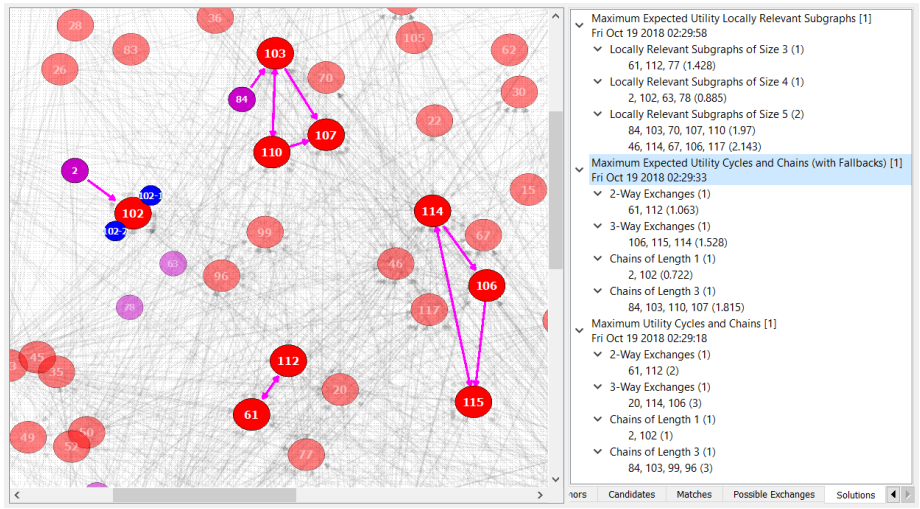
We compare the results obtained through each of the three optimization settings. A utility value of 1 is assumed for each match, and a 0.1 probability of non-viability is assumed for each donor, candidate, and match involved. We allow a maximum cycle size of 3 and a maximum chain length of 4. For LRSs, the maximum size is capped at 5, with the maximum size of sub-cycles and length of sub-chains capped at 3 and 4 respectively.

Figure 5.2 illustrates a representative solution under each optimization scheme. The solution for Cycles and Chains is shown in Figure 5.2(a), consisting of cycles of size 2 and 3 and chains of length 1 and 3 for a total of 9 transplants. Note that there are several possible solutions that admit 9 transplants. While this represents

(a)



(b)



(c)

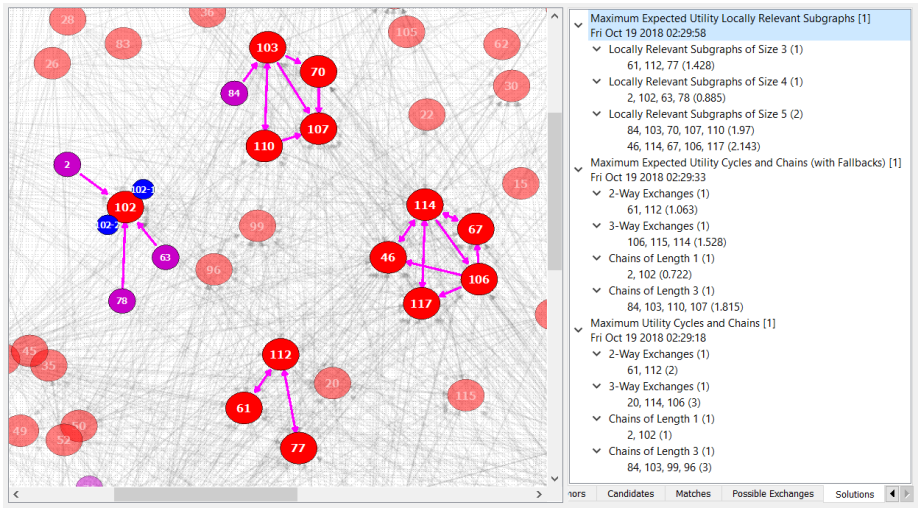


Figure 5.2: KPDGUI solutions produced for a virtual KPD program under three optimization settings: (a) Cycles and Chains, (b) Cycles and Chains with Fallbacks, (c) Locally Relevant Subgraphs

the best-case scenario, it is likely that donors or candidates will not be able to proceed with transplantation despite their selection, or that presumed matches will be overturned by results of a laboratory crossmatch. In either case, the cycle or chain would have to be abandoned or shortened, respectively.

The solution for Cycles and Chains with Fallbacks is displayed in Figure 5.2(b), with the expected utility calculation suggesting that one should expect 5.127 transplants (blind to possible fallback options in the previous setting, aside from sub-chains up to the point of failure for the long chain, one would expect roughly 4.5 transplants). Here the chain from NDD 84 to pairs 103, 110, and 107 figures prominently, with an expected 1.815 transplants after accounting for the possibility of falling back to a sub-chain from NDD 84 to pairs 103 and 107, as well as the potential sub-cycle between pairs 103 and 110.

The solution for the Locally Relevant Subgraph setting, displayed in Figure 5.2(c), groups pair 70 into the chain discussed above, which provides another sub-chain option, increasing the expected number of transplants to 1.97. Another tightly connected subgraph, involving pairs 46, 67, 106, 114, and 117, admits an expected 2.143 transplants, based on the high number of sub-cycles within. The optimal solution produces an expected 6.426 transplants. One may notice that, while we have seen in the previous solution that pair 115 forms a cycle with pairs 114 and 106, this option is not included within a LRS in this solution. This is due to the size constraints imposed on the LRS. The user can either address these situations in an ad hoc manner, or rerun the optimization while allowing for larger LRSs. In either case, one should be aware that solutions will become increasingly complex.

5.4 Discussion

KPDGUI is a flexible tool for visualizing and managing KPD pools, performing optimizations and offering decision support to KPD managers on possible exchanges to pursue. We anticipate that the use of KPDGUI can help continue the adoption and utilization of KPD in transplant centers in the United States and internationally.

We intend to include more streamlined uploading capabilities and further customization and interactivity, based on feedback from clinical collaborators. There are many policy considerations currently being explored in KPD that can be implemented in subsequent versions of KPDGUI. Some of these policy considerations are discussed in Chapter VI.

CHAPTER VI

Summary and Future Work

6.1 Current Issues in Kidney Paired Donation

Several current realities in KPD have yet to be thoroughly explored in the literature from a statistical or operations research standpoint. We briefly overview some of these issues here. Areas of future study in KPD generally focus on expanding the donor pool, addressing barriers to donation, and improving outcomes for patients.

6.1.1 Expansion of Kidney Paired Donation Pools by Including Compatible Pairs

Transplant candidates with compatible living donors can elect to join a KPD program, despite their ability to proceed directly to transplantation. Such pairs may be motivated by the opportunity to find a superior match, for example via a younger donor or a donor with a preferable HLA profile relative to the candidate (Gentry et al., 2007; Mierzejewska et al., 2013; Ferrari et al., 2017; Sönmez and Ünver, 2017). Involvement of compatible pairs enriches the KPD program not only through the addition of donors, but also by potentially offsetting the deficiency of blood type O donors often seen in KPD programs, as these donors are more commonly compatible with their intended recipient. The concept of including compatible pairs in KPD has appeared as early as Roth et al. (2005a).

Convincing compatible pairs of the marginal benefit of participating in KPD represents a major barrier to widespread adoption of this practice (Sönmez and Ünver, 2017). To overcome this barrier, several studies have attempted to develop tools to predict whether an alternative donor, say one participating in KPD, may yield better post-transplant outcomes for a transplant candidate. Ashby et al. (2017) estimate the expected 5- and 10-year graft survival via Cox regression, based on a number of donor, candidate, and match characteristics. Similarly, Massie et al. (2016) extend the Kidney Donor Profile Index, a measure of quality of a deceased donor kidney, to be applicable for living donor kidneys. These estimates can be valuable in the KPD setting to guide decisions for candidates with compatible living donors who may benefit clinically by participating in a KPD program.

Future investigations may seek to model the inclusion of compatible pairs in KPD, where candidates of compatible pairs match with donors expected to provide a superior outcome to their current donors, as measured by the estimated graft survival probabilities of the proposed transplants. Note that compatible pairs can be included in KPDGUI, and we also implement the ability to use the estimated 5- or 10- year graft survival by Ashby et al. (2017) as the utility assignment for potential transplants.

Global Kidney Exchange (GKE) is another mechanism proposed to expand KPD pools via the inclusion of foreign donor-candidate pairs who are unable to proceed with transplantation in their home country due to financial barriers. Such pairs would be invited to the United States to receive a kidney through an exchange with a domestic pair, with all of the associated costs covered by an American institution (Nikzad et al., 2017; Brunner et al., 2017; Rees et al., 2017). GKE is feasible when the cost of dialysis in the developed world exceeds that of kidney transplantation

by an amount greater than the medical costs involved in transplantation for a pair from a developing-world country (Rees et al., 2017). Nikzad et al. (2017) claim that it is possible to finance such transplants in a sustainable way from the savings that arise from taking an American patient off of dialysis. It is further claimed that implementing GKE would reduce the waiting time of domestic patients, as well as the average dialysis cost per patient. The proposal has proven controversial, and there are significant ethical and legal concerns to widespread adoption of the practice, chief among these being the treatment, care and rights of the foreign living donors (Wiseman and Gill, 2017; Baines and Jindal, 2017; Delmonico and Ascher, 2017; Kute et al., 2017).

6.1.2 Transplantation of Incompatible Donor-Candidate Pairs

Outcomes for transplants among blood type incompatible pairs, through a process referred to as desensitization, have become increasingly comparable to those of blood type compatible transplants, in terms of both efficacy and safety (Montgomery et al., 2012; Koo and Yang, 2015; Zschiedrich et al., 2016; Kauke et al., 2016; Masutani et al., 2017). In addition, over the last decade, additional desensitization techniques have made it possible for certain transplants to cross HLA barriers where a compatible donor could not otherwise be found for a transplant candidate (Gentry et al., 2011). These techniques attempt to eliminate or reduce HLA antibody levels in transplant candidates to the point where a successful laboratory crossmatch can be obtained (Pham et al., 2017).

In the KPD context, otherwise incompatible kidney transplantation made possible via desensitization represents an important step in increasing the number of exchange opportunities (Montgomery et al., 2011; Axelrod et al., 2017). However, protocols for desensitization are resource intensive, and patients are at a higher risk of antibody-

mediated rejection and may require more aggressive and costly therapies, meaning desensitization should be reserved for only the most urgent or difficult-to-match candidates (Axelrod et al., 2017). Balancing these objectives in KPD optimization may be of interest for future investigations.

6.1.3 Advanced Donation

In KPD, transplant operations are typically conducted simultaneously, to avoid the possibility of a donor reneging on their commitment after their paired candidate has received their transplant. In some instances, a donor may wish to fulfill their obligation prior to their candidate undergoing transplantation. For some potential donors, time constraints represent an important factor in their decision to donate (Flechner et al., 2015). In fact, the optimal time for some donors to donate may be long before the intended recipient needs a transplant. For example, as presented in Veale et al. (2017), a grandfather may wish to donate a kidney for the future benefit of his grandson with chronic kidney disease. As such, certain accommodations can be made for advanced donation, outside of the traditional restrictions set by KPD programs.

Wall et al. (2017) identify three types of advanced donation. The first is referred to as out-of-sequence donation, where a donor within an identified chain donates early due to time constraints. Their paired candidate receives a kidney shortly thereafter as the earlier section of the chain is completed. For a candidate whose paired donor undergoes out-of-sequence donation, there is the risk that any of the donors in the earlier section of the chain will not be able to proceed with their commitment, leaving the candidate without a transplant and without their paired donor.

The second type of advanced donation is referred to as list exchange, a short-term donation by a donor that occurs before their paired candidate has been matched.

In list exchange, the donor provides a kidney to a candidate on the deceased donor waitlist, with their paired candidate in return receiving future priority on the waitlist (Gentry et al., 2005; Roth et al., 2006; Flechner et al., 2015). It has been suggested that for small populations, more patients can be served by list exchange than KPD, though the role of list exchange may be limited in larger populations due to ethical concerns, namely the disadvantage to blood type O candidates on the deceased donor waitlist (Gentry et al., 2005, 2011).

The third type of advanced donation is referred to as voucher donation, proposed by Veale et al. (2017). In voucher donation, the donor donates a kidney and receives a voucher for certain identified individuals who might require a kidney transplant to be transplanted in the future. Donors in such a program act as NDDs, initiating chains that do not include any of their listed candidates. In the future, when a listed candidate redeems the voucher, the goal would be to end a chain of transplants with the voucher candidate (Ross et al., 2017).

In both list exchange and voucher donation, there is no guarantee for how quickly a kidney will be found for the candidate. In fact, a matched kidney may never become available, or the program may cease to exist. On the other hand, individuals listed in a voucher program may never require a kidney transplant, in which case there is no ethical issue, with the donor simply acting as a NDD (Wall et al., 2017). Ross et al. (2017) acknowledge a number of ethical and logistical issues that can hinder development of a voucher program, most notably how to effectively prioritize candidates redeeming their voucher. Modeling and simulation of voucher programs may help illuminate this process, providing estimates of the benefit and risks to candidates.

6.1.4 Initiating Transplant Chains with Deceased Donor Kidneys

Melcher et al. (2016a) propose initiating transplant chains from deceased donor kidneys, acting in an equivalent manner to NDDs. In practice, a deceased donor kidney is offered to patients on the deceased donor waitlist according to a specified order. Transplant centers can reject the offer, in which case the organ is extended to the next patient according to precedence. If no offer is accepted during the viable timeframe, roughly 36-48 hours after procurement, the organ is discarded. Under this proposal, a deceased donor organ initiates a chain of transplants through a KPD pool, with the final donor returning a transplant to the deceased donor waitlist.

Some ethical issues would need to be considered when initiating chains in KPD using deceased donors. In particular, using deceased donor kidneys in such a manner would need to be disclosed to KPD participants, as they are generally perceived to be of poorer quality, and because the chains would need to be mobilized in a more urgent manner than with living donors (Wall et al., 2017). Responding to Melcher et al. (2016a), Kute et al. (2016) suggest that it may be unfair for certain easy-to-match pairs to receive a deceased donor kidney in exchange for a living donor kidney. Melcher et al. (2016b) reply that such chains may lead to more transplants for difficult-to-match pairs, and that matching algorithms can incorporate exceptions for certain situations. An interesting area of future research would be to determine whether the gains in transplants realized through chains initiated by deceased donors are offset by the lower number of blood type O donors returning to the waitlist, candidates with low priority receiving transplants at the expense of candidates with higher priority on the waitlist, and the possibility of KPD donors reneging on their commitment.

6.1.5 Cooperation between Kidney Paired Donation Programs

While most countries have a single national KPD registry, the United States has several multi-center and single-center KPD programs operating concurrently. This patchwork set-up leads to a number of issues. For example, disruption can occur when a KPD pair enrolled in several KPD registries simultaneously matches in more than one program (Melcher et al., 2013a).

A major issue in KPD in the United States stems from the differing incentives of multi-center KPD programs and the individual transplant centers. While many such centers are involved in larger networks of KPD programs, they may elect to withhold their easy-to-match pairs or NDDs, matching internally in order to maximize the number of its own patients who receive a kidney, and revealing only the more difficult-to-match pairs to the collective (Ashlagi and Roth, 2012; Hajaj et al., 2015; Ashlagi et al., 2015; Toulis and Parkes, 2015). Ashlagi and Roth (2014) summarize the issue by claiming that current matching algorithms do not make it individually rational for transplant centers to reveal all of their pairs. To discourage centers from withholding pairs, it has been suggested to give priority to the most difficult-to-match pairs from centers that have previously formed exchanges through the collective (Ashlagi and Roth, 2012). Hajaj et al. (2015) suggest a mechanism wherein a center that reveals a smaller number of pairs than should be expected at a given time is penalized with a reduced probability that their revealed pairs are included in a collective solution in the future. Further investigations into such strategies, as well as comparisons between global and local KPD solutions, are warranted.

A natural solution to these issues would be the establishment of a national KPD registry in the United States. Simulations by Segev et al. (2005b) suggest that almost half of incompatible pairs could be matched through an optimized national

KPD program, which would provide a greater number and quality of matches than the more regional programs operating currently.

6.1.6 Frequency of Match Runs

There is an intrinsic trade-off between the amount of time a KPD program should wait before evaluating the pool for exchanges, and the number of pairs that can be matched and exchanges that can be arranged. Though it may be costly to do so, waiting for more pairs to accumulate in the pool before identifying potential exchanges tends to increase the number of matches, especially in programs with many highly-sensitized candidates (Ashlagi et al., 2013).

Recently in the United States, however, KPD programs have begun to perform match runs at high frequency, possibly due to competition among programs as described in Section 6.1.5, and recent work has also put into question the conventional wisdom that time should be left between match runs (Ashlagi et al., 2013; Anderson et al., 2015a; Ashlagi et al., 2018). There is some concern that such frequent matching may lead to fewer overall transplants (Fumo et al., 2015). Indeed, situations such as those investigated in Chapter IV, where matches involving difficult-to-match pairs are lost as easy-to-match pairs form exchanges quickly and depart, become more pronounced with more frequent match runs. It appears that the question of optimal timing of match runs is unsettled, and can be an interesting avenue for future investigation.

6.2 Summary

KPD is one of the most important areas for translational research in transplantation, with the number of kidney transplants in the United States arranged through KPD programs rising steadily every year (Organ Procurement

and Transplantation Network). Successful expansion of kidney transplantation through KPD has the potential to greatly improve the quality of life of recipients and reduce costs, compared to continuing dialysis. Improvements to methods and algorithms, expansion of existing allocation strategies and models, and the introduction of new concepts to address current realities in KPD, all serve the goal of improving outcomes for kidney transplant patients and KPD programs.

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